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Methadone

Methadone Maintenance:

A Pharmacist's Guide to Treatment

Edited by
John Brands, MHSc
Eva Janecek, BSc Phm

Centre
for Addiction and
Mental Health
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toxicomanie et
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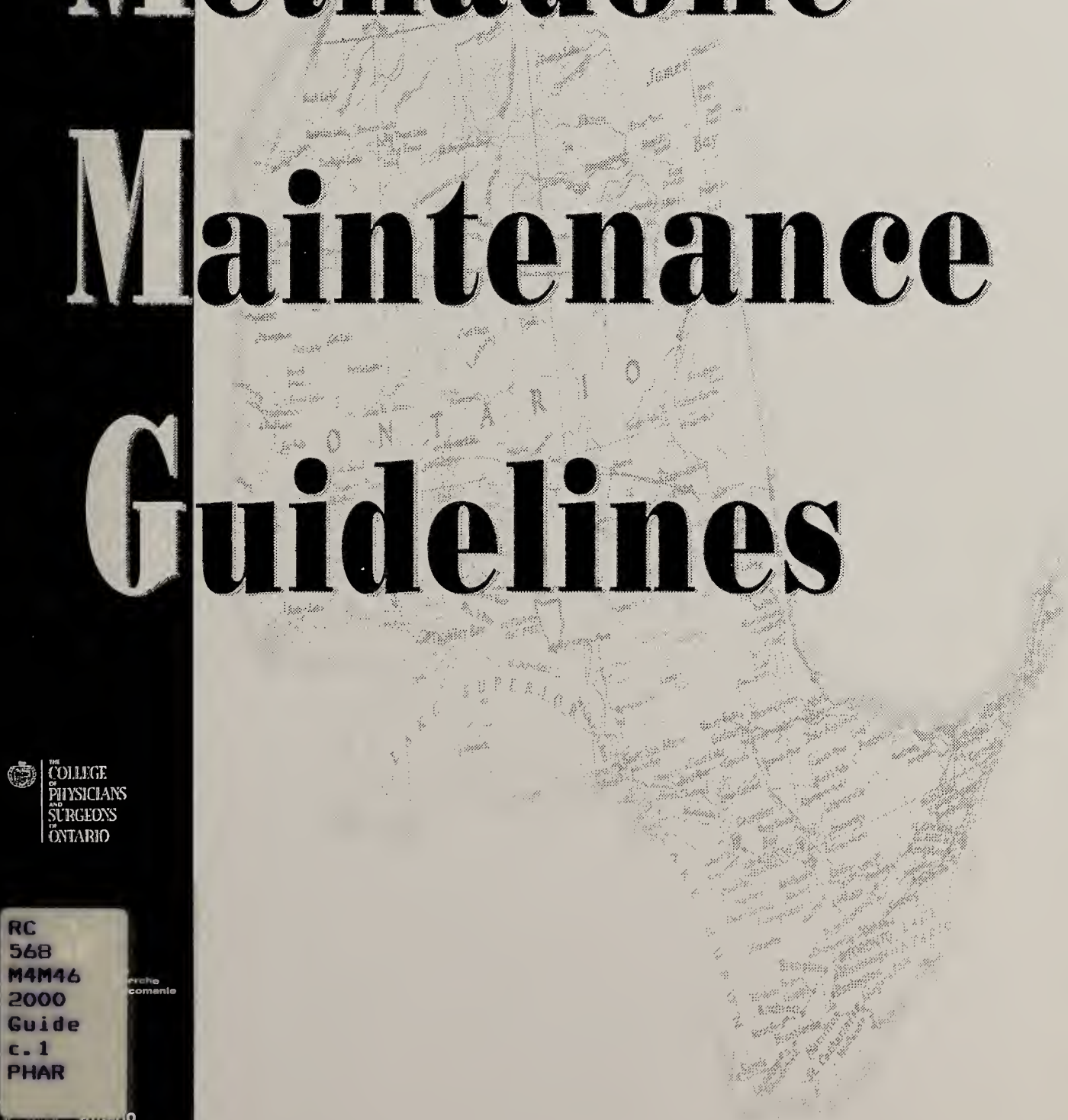
Methadone Maintenance Guidelines



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Methadone Maintenance Guidelines

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PREFACE

The guidelines that follow represent a new standard of practice for Ontario for the prescribing of methadone in the maintenance treatment of opioid dependence. Methadone remains the only opioid approved for long-term pharmacological treatment of opioid dependence.

Where the new guidelines differ, with respect to methadone maintenance treatment, from the direction provided in the 1992 document titled "The use of opioids in the management of opioid dependence" (Bureau of Dangerous Drugs, Health and Welfare Canada), they replace, for Ontario, the 1992 document.

INTRODUCTION

Methadone is a synthetic opioid agonist (i.e. it has actions similar to those of morphine) with good oral biovailability, equipotency with morphine and a long duration of action. Methadone prevents withdrawal symptoms and helps reduce drug cravings in opioid-dependent individuals.

Methadone was developed in Germany at the end of the second world war as a substitute analgesic for morphine. Early research in the late 1940s by Isbell and colleagues at the Addiction Research Center in Lexington, Kentucky, showed that it could also be used to treat withdrawal symptoms in heroin-dependent individuals. In the early 1960s, Dole and Nyswander demonstrated the feasibility of using methadone as a maintenance medication.

Methadone maintenance involves the daily administration of methadone over an extended period as an oral substitute for heroin or other morphine-like drugs to opioid-dependent individuals. A single dose administered to a stabilized individual lasts between 24 to 36 hours without causing euphoria, sedation or analgesia. This enables individuals to function normally and to perform mental and physical tasks without impairment. In sufficient doses, cross-tolerance to other opioids develops, i.e. methadone "blocks" the euphoric effects of self-administered illicit opioids.

Numerous studies have shown that maintaining opioid-dependent individuals on methadone has many benefits including:

- decreased illegal activity
- increased employment
- reduced illicit drug use

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- improved health status
- increased cost-effectiveness

Conversely, illicit opioid use has been associated with:

- illegal activity
- unemployment
- family disruption
- illnesses such as HIV/AIDS, hepatitis B and C, tuberculosis and sexually transmitted diseases
- death.

Traditionally, methadone maintenance programs have been abstinence-oriented, with the expectation that patients refrain from all non-prescription drug use. Urine screening has been used as a primary means of determining compliance. Patients have also been required to participate actively in psychosocial treatment. While abstinence-based approaches have been effective in assisting opioid users who are seeking to withdraw gradually from opioids via methadone and who are committed to a drug-free lifestyle, recent developments in Ontario have necessitated a fundamental rethinking of service delivery goals and practices for the opioid-dependent patient. First, the risk of HIV infection from intravenous drug use has increased the acceptability of long-term methadone maintenance treatment. Second, there has been an increase in the number of patients presenting for treatment who list heroin as their primary drug of abuse. Finally, many of these individuals are turning to treatment providers requesting methadone treatment.

While not all opioid-dependent individuals are interested in or appropriate candidates for methadone treatment, a considerable gap exists between the demand for methadone treatment and its availability. There is also strong support for developing new models of methadone treatment that are not abstinence-based in order to serve a wider range of opioid users, including those who are not able to achieve abstinence.

CRITERIA FOR ADMISSION

a) Individuals must meet criteria set out in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) for opioid dependence.

b) Individuals should be 18 yrs. of age or older.

c) There should be evidence of extensive past opioid use and/or failed treatment attempts. *Previous unsuccessful methadone treatment should not exclude a patient from methadone treatment.*

d) There should be at least one urine drug screen positive for opioids prior to initiating methadone treatment.

ASSESSMENT

a) Informed Consent

Informed consent must be obtained *prior* to initiating the assessment process.

b) Medical Assessment

A medical assessment must be done *prior* to admitting an individual to a methadone maintenance program. The purpose of the assessment is to:

- determine a patient's suitability for methadone treatment (i.e. establish a

diagnosis of opioid dependence)

- screen for medical complications associated with drug use (Hep B, Hep C, HIV/AIDS, TB) including informed consent and pre- and post-test counselling procedures
- identify other medical or psychiatric conditions/problems
- identify factors that put the individual at risk for harm (e.g., unsafe sexual practices, emotional or physical abuse, lack of birth control, suicidal ideation, etc.)
- recommend a treatment plan to the patient

c) Psychosocial Assessment

The psychosocial assessment should be done as proximal to the medical assessment as possible. It should be repeated as often as necessary during the course of treatment. The use of a well-validated instrument (e.g., the Addiction Severity Index) is recommended. The purpose of the assessment is to:

- gain an overview of problems in life functioning and establish baseline data across various areas (medical, legal, drugs, alcohol, employment, family/social, psychiatric)
- identify psychosocial issues that require referral
- establish a treatment plan, outlining objectives and conditions/expectations

The assessment process should be viewed as an opportunity to provide patients with feedback in order to motivate them to avoid high risk behaviours and to support lifestyle changes.

d) Treatment Agreement

In order to ensure that all patients receiving methadone substitution have a clear understanding of their responsibilities and obligations as partners in the treatment process, all patients should sign a program treatment agreement prior to receiving their first dose of methadone.

If the patient is requesting treatment for their opioid dependence at an addiction treatment centre that does not offer comprehensive medical care, the treatment agreement should also specify that the physician who prescribes methadone for them does not offer such care. Patients should be informed that it is their responsibility to arrange to have a family physician. If the patient requests assistance, a staff member should be delegated to help. Certain clinical situations (e.g., pregnancy) require special consideration. Refer to the Clinician's Manual for Methadone Treatment for advice on such situations.

The patient should receive an orientation to the program including information about methadone. The patient should be given an opportunity to ask questions about methadone or any other currently prescribed drug.

The treatment agreement should be signed by the patient in duplicate – one copy to be retained by the patient and the other copy to be placed in the patient's health record.

METHADONE DOSING ISSUES

a) Methadone Dose Stabilization

The initial dose of methadone is administered after the medical assessment has been completed and a diagnosis of opioid dependence has been established. The following protocol is suggested:

- the initial dose should be 15 - 30 mg of methadone per day

- dose adjustments should be made every 3 - 4 days until the patient is comfortable or a total daily dose of 60 mg has been reached
- after 60 mg, dose changes (5 - 10 mg) should only be made every 7 days if needed; if the patient is receiving 80 mg of methadone or more and continues to use drugs, complains of withdrawal and/or urges to use, the physician should reassess the patient
- criteria for dose increases include:
  a) signs and symptoms of withdrawal (objective and subjective)
  b) amount and/or frequency of drug use not decreasing
  c) persistent cravings for opioids

b) Maintenance

Once a patient has been stabilized on methadone, dose changes may be made only after the physician has reassessed the patient.

Although maintenance doses of methadone should be individualized to suit each patient research evidence suggests that (as a general rule) higher doses of methadone (>60mg) are associated with better retention rates in treatment and greater decreases in heroin use.

c) Missed Doses

If a patient does not attend on three consecutive days to drink his/her methadone dose, he/she should be reassessed by the physician before being medicated. For additional information refer to the Clinician's Manual for Methadone Treatment.

d) Deferral To Medicate

Patients should not be medicated if they appear to be intoxicated; patients may be asked to wait to be reassessed at a later time.

COUNSELLING

There is strong evidence to support improved treatment outcomes when methadone maintenance includes counselling services. The program reserves the right to determine counselling requirements on an individual patient or program-wide basis. Additional information on counselling may be found in the Clinician's Manual for Methadone Treatment.

URINE TOXICOLOGY SCREENING

a) Urine toxicology screens are done to ensure that the patient is ingesting the methadone that is prescribed for them and to detect whether they are taking any other non-prescribed drugs. As a general rule, the validity of the urine screen results increases if the collection is done under supervision.

b) A minimum of one urine drug screen is advised prior to initiation of methadone treatment.

c) Urine samples should be tested twice weekly during the methadone dose stabilization period (usually the first 8 weeks of treatment)

d) Once a patient is considered to be "functionally stable" (please refer to "Carry or Take-home Medication" below for the definition of functional stability), the physician may set a weekly or twice monthly urine testing schedule depending on the patient's progress. In this instance, a random schedule is recommended.

e) Patients who are functionally stable for a one year period (i.e. one year of drug-free urine samples) may leave one urine sample monthly. A random schedule is strongly recommended.

f) If the presence of illicit drugs and/or unexplained absence of methadone or its metabolites is detected following the schedule outlined in d) and e), (vide supra), the twice weekly urine testing schedule may be reinstated for a specified period of time.

g) The physician has the right to request additional urine samples at any time. This should be clearly stated in the program treatment agreement.

CARRY OR TAKE-HOME MEDICATION

Carry or take-home medication may be used as a therapeutic tool to assist patients in re-establishing their lives along more constructive lines.

a) Carry or take home medication is not recommended during the first three months of treatment (see Table 1).

b) Carry or take-home medication may be given to patients who are considered to be functionally stable. Stability may be assessed by a measured consideration of behavioural and other criteria, including the following:

1) program participation:
- attends as required for methadone
- attends scheduled appointments
- complies with treatment agreement

2) cognitive stability including the ability to assume responsibility for the care of the medication and to use it as prescribed

3) abstinence or non-harmful use of drugs (harm can be seen as a continuum and can result from a single use or from long term use of drugs, measurable in four basic ways: physiological, psychological, inter-personal/social, and societal)

4) social integration, including: employment, school attendance, child care responsibilities, volunteer work.

c) A suggested schedule for granting carry medication is outlined in Table 1.

d) Patients who are eligible for and receive carry medication must accept responsibility for the take-home methadone doses (which includes the safe-keeping of the medication) and use them for their intended purposes.

e) Patients who have take-home medication should be informed that they may be asked at any time to appear in the clinic and bring with them the remainder of their carry medication. This procedure is used to deter patients from diverting their methadone doses.

f) Carry medication may be cancelled at any time by the prescribing physician if he/she believes that the safety of the patient or that of others is at risk. Situations where the cancellation of carry medication might be considered are as follows:

- reasonable evidence that the patient has failed to meet the terms of the treatment agreement
- sustained use of unauthorized drugs
- the patient has produced an unacceptable urine sample or has tampered with the collection of his/her required urine sample (for example, but not limited to substituting another person's urine or some other material for his/her own urine; adding some contaminant to the urine sample submitted; providing a previously collected (i.e., "stale") sample of his/her own urine instead of a fresh sample collected under supervision; diluted his/her own urine sample)
- the patient has approached another methadone-treated patient suggesting or proposing to sell, buy or share any urine sample, or to tamper with any urine sample
- the patient has diverted, or allowed to be diverted, any part of his/her methadone (i.e., has failed to consume part or all of the methadone dose prescribed for him/her and allowed it to become available for use by anyone else)
- the patient has approached another methadone-treated patient suggesting or proposing to sell, buy or share methadone

Exceptions to the Carry Criteria

It is recognized that occasions will arise where an extension of the regular carry arrangements may be appropriate, such as:

- annual vacation to areas where methadone is not readily available
- compassionate leave
- out-of-town employment opportunities

It is the responsibility of the prescribing physician to decide whether to approve the request. Once this decision is made, the carry medication days may be extended beyond 6 days to a limit of 14 days. Alternatively, the prescribing physician may suggest pick-up in a community pharmacy in lieu of the extension beyond the 6 days.

INVOLUNTARY DISCHARGE

While a comprehensive treatment system would have options and levels of care that are appropriate for the diverse range of individuals who are opioid dependent, specific programs and practitioners have the right to determine who they will treat and to discharge or to transfer a patient to another program/physician if deemed necessary. If the decision is made to discharge a patient from treatment, the general guidelines issued by the College of Physicians and Surgeons of Ontario (CPSO) for ending doctor-patient relationships should be followed.

It is important to balance the needs of the patient for care with other issues including program standards and the safety of other individuals when considering involuntary discharge.

Involuntary discharge from methadone treatment will be considered when evidence indicates that the following has occurred:

a) Threats:

- the patient has threatened the safety or well-being of a staff member or another patient by oral or written action;

b) Disruptive Behaviour:

- the patient has engaged in disruptive behaviour on the premises;

c) Violent Behaviour:

- the patient has engaged in violent behaviour towards a staff member, a patient or another person;

d) Illegal Activity:

- the patient has engaged in an illegal act on the premises;

e) Diversion of Methadone:

- the patient has diverted, or allowed to be diverted, any part of his/her prescribed methadone;

f) Failure to Meet Program Criteria:

- the patient has failed to meet criteria for continuation in methadone substitution treatment, i.e., the patient has not adhered to the criteria outlined in the treatment agreement;

g) Contraindication of Methadone:

- methadone has become contraindicated for the patient, in the opinion of the prescribing physician;

h) Missed Medication:

- the patient has failed to pick up doses of methadone for 3 consecutive days, unless alternative arrangements for pick-up have been previously made (e.g., vacation privileges, community pharmacy pick-up arrangements) or there is convincing evidence that the failure to pick up was beyond the patient's control.

TABLE 1

Level	Characteristics	Take Home Medication Days	No. Of Doses
Level I	Patient has been in a treatment program for 3 months and the patient is functionally stable for the last 4 weeks.	Sunday Statutory Holidays	1 take home dose
Level II	Patient has been in a treatment program for 3 months; no unauthorized drug use for the last month and is functionally stable for the last 4 weeks. or Patient has been in a treatment program for 6 months; urine screens show occasional drug use - but the patient is otherwise stable.	Wednesday Saturday, Sunday Statutory Holidays (same as above)	3 take home doses
Level III	Patient has been in a treatment program for 6 months; no unauthorized drug use for the last month and is functionally stable. or Patient has been in a treatment program for 12 months or longer; urine screens show occasional drug use - but the patient is otherwise stable.	Monday/Tuesday Wednesday Thursday/Friday Saturday, Sunday, Statutory Holidays (same as above)	5 take home doses
Level IV	Patient has been drug-free for 12 months and is functionally stable	attend once a week	6 take home doses

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CONTENTS

About the Authors vii

Acknowledgments viii

A Message from the Ontario College of Pharmacists ix

Introduction 1

How to Use This Guide 1

Chapter 1 **Substance Dependence and Opioid Dependence** 3
Substance Dependence and Addiction 3
Opioid Dependence 3
Opioid Abuse 5
Determinants of Dependence 5
Misconceptions about Substance Dependence 8
Non-medical Use of Opioids 9
Opioid Tolerance and Cross-Tolerance 12
Physical Dependence and Withdrawal 12
Opioid Withdrawal Management (Detoxification) 13

Chapter 2 **Overview of Methadone Maintenance Treatment** 17
The Rationale for Methadone Maintenance Treatment 17
The Potential Benefits of Methadone Maintenance Treatment 17
The Potential Disadvantages of Methadone Maintenance Treatment 19
Alternative Treatments for Opioid Dependence 20
The Effectiveness of Methadone Maintenance Treatment 21
The Components of Methadone Maintenance Treatment 22
The Treatment of Pain in the Context of Illicit Opioid Use and Methadone Maintenance Treatment 28
The Regulation of Methadone Maintenance Treatment in Ontario 29
Methadone Diversion 30
Methadone Maintenance Treatment As a Harm Reduction Strategy 32
The Availability of Methadone Maintenance Treatment 34

Chapter 3 **METHADONE** **37**
The Structure of Methadone 37
The Effects of Methadone and Other Opioids 38
The Safety of Methadone 38
Methadone Pharmacokinetics 41
The Differences between Heroin and Methadone 43

Chapter 4 **PRESCRIPTIONS IN COMMUNITY PHARMACIES** **45**
Legislative Framework 45
Authorization 45
Prescription Requirements 46

Chapter 5 **PREPARATION AND STORAGE** **51**
Summary 51
Availability 51
Preparation of Stock Solution 51
Stability of Stock Solution 52
Preparation of Final Dosage Form 52
Stability of Final Dosage Form 53

Chapter 6 **METHADONE DOSING ISSUES** **55**
Initial Dose 55
Initial Stabilization 55
Maintenance Dose 56
Timing of Doses 56
Divided Doses 56
Missed Doses 57
Vomited Doses 58
Dosing in Pregnancy 58
Methadone Discontinuation 59

Chapter 7 **DISPENSING AND OBSERVED SELF-ADMINISTRATION** **61**
Communication 62
Methadone Dispensing Area 66
Patient Identification 66
Supervised Ingestion 66
Intoxicated Patients 67
Documentation 68
Requests to Dispense to a Person Other Than the Client 68
Home Delivery 68
Guest Dosing 69
Take-Home Doses (Carries) 69
Patient-Pharmacist Agreements/Contracts 72

Chapter 8 DIVERSION 75
Pharmacy Tips to Minimize Diversion 76

Chapter 9 CONTINUITY OF CARE WHEN PATIENTS ARE INSTITUTIONALIZED 79
Communication 80
Temporary Authorization for Physicians 81
Provision of Methadone in Hospitals and Prisons 81

Chapter 10 METHADONE: ADVERSE EFFECTS, TOXICITY, OVERDOSE AND WITHDRAWAL .. 85
Adverse Effects 85
Opioid/Methadone Intoxication and Overdose 89
Opioid/Methadone Withdrawal 91

Chapter 11 DRUG INTERACTIONS 93
Pharmacodynamic Interactions 93
Pharmacokinetic Interactions 93
Medications That Are Contraindicated Because They Can Precipitate Withdrawal 95
Medications That Can Decrease Plasma Levels of Methadone 96
Medications That Can Increase Plasma Levels of Methadone 97
Other Interactions 99
Interactions with Food 99

Chapter 12 METHADONE MAINTENANCE UNDER SPECIAL CIRCUMSTANCES 103
Pregnant Patients 103
Patients with HIV/AIDS 105
Treatment of Acute Pain in Methandone Maintenance Treatment Patients 105
Disruptive Behaviour by Patients 106

Appendix 1 METHADONE MAINTENANCE THERAPY: INFORMATION FOR CLIENTS 109
Appendix 2 SAMPLE METHADONE MAINTENANCE TREATMENT AGREEMENT 113
Appendix 3 SAMPLE METHADONE CARRY AGREEMENT 115
Appendix 4 SAMPLE REMINDER ABOUT METHADONE CARRIES 117
Appendix 5 SAMPLE METHADONE PRESCRIPTION FORM 119
Appendix 6 MANAGEMENT OF METHADONE OVERDOSE: AN OVERVIEW 121
Appendix 7 ENDING THE PHARMACIST/PATIENT RELATIONSHIP (REPRINT FROM PHARMACY CONNECTION) 133
Appendix 8 USE OF METHADONE FOR THE TREATMENT OF CHRONIC PAIN 137

About the Authors

Bruna Brands, PhD, is a clinical trials scientist in the Clinical Research Department at the Centre for Addiction and Mental Health (CAMH). She is the lead editor of *Management of Alcohol, Tobacco and Other Drugs: A Physician's Manual*, and co-edited *Drugs and Drug Abuse and Methadone Maintenance: A Physician's Guide to Treatment*.

John Brands, MHSc, co-edited *Methadone Maintenance: A Physician's Guide to Treatment*.

Pearl Isaac, BSc Phm, is a pharmacist at CAMH, and is a pharmacy consultant with the Addiction Clinical Consultation Service (ACCS). She is involved in various educational activities and is an author of numerous publications about substances of abuse and treatment from the pharmacist's perspective

Eva Janecek, BSc Phm, at the time of the guide's preparation was Head of Pharmacy Services at CAMH, and a pharmacy consultant with ACCS. She is a senior lecturer at the Faculty of Pharmacy, University of Toronto and is involved in various educational activities at CAMH. She is an author and reviewer of numerous publications in the area of substance dependence.

Anne Kalvik, BSc Phm, is a pharmacist at CAMH and a pharmacy consultant with ACCS. She is involved in various educational activities and is an author of numerous publications about substances of abuse and treatment from the pharmacist's perspective.

David Marsh, MD, is the Clinical Director of the Addiction Medicine Program, CAMH and Assistant Professor, Department of Psychiatry, Faculty of Medicine, University of Toronto.

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James A. Gay, *Manager*, Pharmacy Practice Programs, Ontario College of Pharmacists
Peter Selby, *Medical Consultant*, Addiction Medicine Clinic, CAMH
Christine Harris, *Production Co-ordinator*, Communications and Marketing, CAMH
Andrew Johnson, *Product Developer*, Communications and Marketing, CAMH
Nancy Leung, *Creative Service Co-ordinator*, Communications and Marketing, CAMH
Myles Magner, *Editorial Services Co-ordinator*, Communications and Marketing, CAMH
Sue McCluskey, *Editorial Services Co-ordinator*, Communications and Marketing, CAMH
Jackie Nourse, *Departmental Secretary*, Communications and Marketing, CAMH
Victoria Taylor, *Creative Services*, Communications and Marketing, CAMH

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Ontario College of Pharmacists

A Message from the Ontario College of Pharmacists:

The Ontario College of Pharmacists welcomes the publication of *Methadone Maintenance: A Pharmacist's Manual*. As a component of the methadone maintenance training offered by the Centre for Addiction and Mental Health (CAMH), the manual will serve as a valuable tool for pharmacists after they have completed the Methadone Maintenance Workshop. The OCP endorses the CAMH methadone maintenance training program and encourages pharmacists who dispense methadone to patients to take advantage of this professional training.

The effectiveness of methadone maintenance as a treatment for opioid dependence is well-established. Because methadone allows individuals to function normally and to perform mental and physical tasks without impairment, methadone maintenance helps individuals, who are often socially marginalized, to meaningfully re-enter the community. We also recognize the value of methadone maintenance as a strategy for reducing such drug related harm as the spread of HIV and other infectious diseases due to needle-sharing.

Clearly, *Methadone Maintenance: A Pharmacist's Manual* reflects an understanding of the essential role that pharmacists play in patient focused care. It recognizes that pharmacists can and should be seen as important partners in the continuum of patient treatment and that they can have a positive influence on treatment outcomes in the community.

The Ontario College of Pharmacists is proud to be a partner in the provincial planning and co-ordination of activities for the enhancement on methadone services in Ontario.

James A. Gay, B.Sc. Pharm.
Manager, Pharmacy Practice Programs
jag0191

483 HURON STREET, TORONTO, ONTARIO, M5R 2R4 • TELEPHONE: (416) 962-4861 • FACSIMILE: (416) 962-1619
WEBSITE: http://www.ocpharma.com • email@ocpharma.com

INTRODUCTION

The provision of pharmacy care is an integral component of methadone maintenance treatment (MMT). Pharmacy staff have more contact with the patient than anyone else on the treatment team. Many patients go to the pharmacy daily for their medication, especially at the beginning of treatment. The patients therefore have an opportunity to form an important relationship with their pharmacist. In turn, the pharmacist has an opportunity to offer encouragement and support as the patient progresses through treatment for opioid dependence.

The dispensing pharmacist is at the front line of treatment and can have a real impact on patient outcome. Pharmacists are in a pivotal position to make note of important information and communicate it to the prescriber. Information regarding compliance, intoxication or impairment, and improving or deteriorating self-care, is extremely valuable to the prescribing physician and the treatment team. They depend on such information when assessing the efficacy of treatment and making important therapeutic decisions.

How to Use This Guide

Methadone Maintenance: A Pharmacist's Guide to Treatment provides pharmacists with a comprehensive overview of MMT and focuses on issues of special importance to busy working pharmacists. The first three chapters provide an in-depth introduction to clinical issues of Opioid Dependence and cover important concepts such as the clinical criteria for dependence, opioid tolerance, cross-tolerance and withdrawal management. The rationale for providing methadone maintenance treatment and the components of the treatment are also detailed. The third chapter focuses specifically on methadone as a drug and covers its effects, known side-effects, opioid intoxication, opioid withdrawal, the pharmacokinetics of methadone and the distinction between methadone and heroin.

Chapters 4 through 12 focus primarily on pharmacy-related issues. It is this section of the guide that will be most useful in everyday pharmacy practice when methadone-related issues arise. Important topics covered in these chapters include physician

authorization for prescribing methadone, guidelines for the appropriate writing of methadone prescriptions, proper preparation and storage of methadone, and dosing issues (including induction, maintenance and tapering). The procedures involved in dispensing methadone to a MMT patient are also covered. They include dealing with new patients, the importance of good pharmacist-patient communications, observing methadone self-administration and dispensing take-home doses. Among other important issues discussed are provision of care to institutionalized patients, information relating to the potential adverse effects of taking methadone, the toxicity of methadone and the related issues of overdose and withdrawal. Drug interactions are covered in Chapter 11, including a comprehensive list of contraindicated medications. The last chapter focuses on special circumstances, such as dispensing methadone to pregnant patients or to those with HIV/AIDS.

chapter

1

Substance Dependence and Opioid Dependence

John Brands, MHSc
Bruna Brands, PhD
and David Marsh, MD

SUBSTANCE DEPENDENCE AND OPIOID DEPENDENCE

An understanding of methadone maintenance treatment (MMT) relies on a clear conception of substance dependence in general and opioid dependence in particular. This chapter provides an overview of substance dependence and opioid dependence, and ends with a brief description of the non-medical use of opioids.

Substance Dependence and Addiction

Definition

What is commonly referred to as *addiction* to nicotine, alcohol or other drugs is defined as Substance Dependence in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). Developed by the American Psychiatric Association, the DSM-IV is a widely recognized diagnostic system designed to increase uniformity in the use of psychiatric terminology. In this context, addiction and Substance Dependence are one and the same, as are opioid addiction and Opioid Dependence. The use of the term *substance* instead of *drug* highlights the similarities between dependence on licit drugs not commonly referred to as such (e.g., nicotine, alcohol) and dependence on illicit drugs (e.g., heroin).

Opioid Dependence

Substance Dependence, including Opioid Dependence, is typically (but not inevitably) a long-lasting and relapsing disorder that causes significant distress and disability. It is also characterized by specific long-lasting abnormalities in brain structure and function, accompanied by long-lasting compulsive drug seeking and use. Like many other chronic illnesses, Substance Dependence is also treatable.

To be considered for MMT in Ontario, individuals must meet DSM-IV criteria for Opioid Dependence.

Criteria for Opioid Dependence*

A maladaptive pattern of opioid use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occuring at any time in the same 12-month period:

1. **tolerance, as defined by either of the following:**
   a) a need for markedly increased amounts of the opioid to achieve intoxication or desired effect
   b) markedly diminished effect with continued use of the same amount of the opioid
2. **withdrawal, as manifested by either of the following:**
   a) the opioid withdrawal syndrome
   b) the same (or a related) opioid is taken to relieve or avoid withdrawal symptoms
3. **the opioid is often taken in larger amounts or over a longer period than was intended**
4. **there is a persistent desire or unsuccessful efforts to cut down or control opioid use**
5. **a great deal of time is spent in activities necessary to obtain the opioid, use it and recover from its effects**
6. **important social, occupational, or recreational activities are given up or reduced because of opioid use**
7. **the opioid use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the opioid.**

It should be noted that opioid tolerance and/or opioid physical dependence as manifested by withdrawal is/are insufficient to define Opioid Dependence. For example, cancer patients receiving morphine for severe pain will develop tolerance to some of its effects, and will show the signs and experience the symptoms of opioid withdrawal if the medication is abruptly discontinued. Nevertheless, only rarely will such patients exhibit compulsive use. Furthermore, such patients would not be described as dependent on (or "addicted to") morphine and would not be

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treated for morphine dependence (or morphine "addiction"). The necessary defining characteristic of Opioid Dependence is compulsive opioid use as described above by DSM-IV criteria three to seven. Compulsive opioid use almost always leads to opioid tolerance and to physical dependence as manifested by withdrawal.

Opioid Abuse

In the DSM-IV, Opioid Abuse is distinguished from Opioid Dependence. Individuals who meet criteria for abuse typically use opioids much less often than those who are opioid-dependent. They do not exhibit a pattern of compulsive opioid use, and do not exhibit clinically significant tolerance and physical dependence as manifested by withdrawal. To meet criteria for abuse, opioid use must be recurrent and have adverse consequences. Opioid Abuse generally has fewer and less severe adverse consequences than Opioid Dependence. Opioid Abuse is also much more common than Opioid Dependence, and many individuals who exhibit Opioid Abuse will not become dependent on opioids. While individuals who exhibit Opioid Abuse may seek and be considered for treatment, they are not candidates for MMT.

Determinants of Dependence

The development and the maintenance of Substance Dependence, including Opioid Dependence, involves psychological, social, biological and drug factors, and effective prevention and treatment must address all causes/components (Leshner, 1997). From a psychological perspective, the development and maintenance of Substance Dependence has been described in terms of adaptive attempts to alleviate emotional suffering and to repair related self-regulatory deficiencies that may include impaired self-care, vulnerabilities in self-development and self-esteem, troubled self-object relations and deficits in affect tolerance (Jaffe et al., 1997). Other psychological determinants of Substance Dependence involve personality and conditioned responses.

From a social perspective, to the extent that individuals "choose" to use drugs, such a choice is determined in part by the legal controls that influence drug availability and price. Social norms, and the influence of family, friends, schoolmates and teachers, workmates, employers and other role models are also fundamental factors influencing substance use. Critical, too, are the availability of alternative sources of positive reinforcement, including social and economic opportunities (McKim, 1997), and opportunities for recreation offering pleasure and diversion. Adverse developmental experiences with family, school or peers, which involve lack of guidance, rejection and physical, emotional and sexual abuse, are also factors in substance use.

The maintenance of dependence on illicit drugs has been associated with drug-use rituals that give stigmatized and marginalized users a feeling of contact, interaction, belonging (albeit to a deviant group) and identity (Grund, 1993). "Stress" has been identified as a determinant of relapse to drug use following a period of abstinence (Leshner, 1997), and post-traumatic stress disorder is not uncommon among patients dependent on opioids. Social factors help explain the high incidence of Substance Dependence associated with poverty, homelessness, unemployment and social decay in urban areas, prisons and battle zones.

There is also some evidence suggesting that biological factors contribute to opioid use. Pharmacological factors are explained in terms of abuse/dependence liability.

Different definitions of Substance Dependence and different approaches to its prevention and treatment reflect different opinions as to its cause. A recent explanation of drug use is that individuals use alcohol and other drugs primarily to feel good ("sensation-seeking") or to feel better ("self-medication," e.g., for anxiety, depression) (Leshner, 1998). Yet older views on Substance Dependence still influence the way we think about it and the language we use when we talk about it.

One of these older views is that people who become dependent on drugs are deficient in character and will. They are seen as weak and bad, as sinners and criminals. The problem of substance dependence is thus left to clerics and to police officers to deal with, and "treatments" feature censure, confession, prayer and punishment. While this view is still with us, it is now recognized that substance dependence is a health issue — a medical condition with implications for individual and public health — that can be effectively dealt with by health care professionals.

Another older view is that substance dependence is a condition sustained and worsened primarily by fear of withdrawal when the substance use is discontinued, with withdrawal being defined in terms of its objective signs. This view draws attention to substances that are associated with relatively severe withdrawal signs (e.g., opioids) and implies that these substances are "more addictive." This narrow perspective is inconsistent with the recognition of very severe and very harmful dependence on substances associated with withdrawal signs that are generally much less severe (e.g., cocaine) (McKim, 1997). This older view reflects a focus on the substance as the problem (and consequently on "detoxification" as a "cure") that is gradually being replaced by a focus on the nature and the amount of harm suffered by the user and the community.

Severity and Adverse Consequences

When looking at Substance Dependence as a problem from individual and societal perspectives, it is essential to look beyond its mere presence or absence to its severity and its adverse consequences. The criteria listed in the DSM-IV define the presence/absence of Substance Dependence and its severity (see the specific example of Opioid Dependence above). Substance Dependence is present when an individual meets a minimum number of these criteria; it is more severe when additional criteria are met. The adverse consequences of Substance Dependence are closely related to, and almost inseparable from, its severity. The severity of Substance Dependence, and the number and seriousness of its adverse consequences at a particular point in time, can vary markedly among dependent individuals. The severity and consequences can depend, among other things, on the dependent individual's income level. The consequences of Substance Dependence are also related to the mode of drug administration. For example, fewer serious health effects would accompany nicotine dependence if it did not usually involve inhaling the products of tobacco combustion. Likewise, fewer serious health effects would accompany dependence on heroin if it were not usually injected.

The severity of Substance Dependence, and the number and seriousness of its adverse consequences, can also vary with the legal status of the drug. Most legal non-medicinal psychoactive drugs (e.g., nicotine, alcohol) are much cheaper and more easily available than illegal non-medicinal psychoactive drugs. At the societal level, low prices and wide availability of legal non-medicinal drugs result in much higher rates of dependence and much higher costs compared with those related to the use of illicit drugs. At the level of the individual user, however, dependence on illicit substances often leads to more severe adverse consequences. Individuals dependent on nicotine or alcohol do not risk incarceration for possession and may very well be able to predictably avoid withdrawal and satisfy their craving, even on modest incomes. In contrast, dependence on illicit substances, particularly among individuals with relatively low incomes, is likely to be associated with illegal and other socially disruptive behaviour. Social factors also influence the expression of Substance Dependence. Similar rates of Substance Dependence are seen across social class and status. Nevertheless, its determinants, the substances involved, the severity of dependence, and the number and seriousness of its adverse consequences, are different for different social groups. Components that define the severity of Opioid Dependence and its adverse consequences are discussed above under "Opioid Dependence," and in Chapter 2 under "The Rationale for Methadone Maintenance Treatment."

Relative Abuse/Dependence Liability

Although societal factors, such as price and availability, influence the development and maintenance of Substance Dependence, substances such as nicotine, heroin and cocaine have a greater dependence liability than others (e.g., LSD). The pharmacological action of the drug and the route of administration determine the dependence liability, or the degree to which use of a particular substance will lead to Substance Dependence. All substances of abuse share similar pharmacological actions that allow them to act as reinforcers. A drug is reinforcing if its effects influence behaviour in a way that increases the likelihood of repeated use. Human and animal experiments have carefully delineated the network of brain structures and neurotransmitters underlying the reinforcing properties of drugs. Furthermore, animal experiments predict the strength of a drug's reinforcing properties in human beings. The route of administration influences the dependence liability of a substance by affecting the rate at which the drug is delivered to the brain. In general, drugs that are inhaled or injected are more likely to lead to dependence than those taken orally.

Misconceptions about Substance Dependence

A common misunderstanding is the idea that Substance Dependence is a "self-imposed" condition, when compared with other medical conditions. Often implied is that those who suffer from Substance Dependence are not as deserving of treatment as those who suffer from other conditions. Censure and punishment are perceived to be more appropriate. Yet blaming the dependent individual may only amount to blaming the victim. Many of the determinants of Substance Dependence (discussed above under "Substance Dependence and Addiction") are not within the control of the individual suffering from it. Furthermore, Substance Dependence is no more "self-imposed" than, for example, diseases associated with unhealthy lifestyles (e.g., cardiovascular disease associated with obesity resulting from poor diet and/or inadequate exercise), many instances of sexually transmitted disease, or injuries sustained in the course of engaging in physically hazardous recreational activities and sports. Unlike these other medical conditions, Substance Dependence, particularly dependence on illicit drugs (and particularly when these are injected), is socially unacceptable.

Non-medical Use of Opioids

Sources and Use

Some opioids, used non-medically for their psychoactive effects, have been manufactured by pharmaceutical firms for medical use, whereas others have been prepared specifically for non-medical use.

Opioids manufactured for medical use may be diverted for the illicit market, or for personal use, through theft from manufacturers, wholesalers or retailers, or from shipments in transit. Alternatively, diversion to the illicit market may take place through forging opioid prescriptions or obtaining opioid prescriptions from physicians under false pretences (e.g., by giving physicians false histories of pain). Most of this diverted medication is in oral dosage form that may be used orally or altered for injection. Opioids commonly diverted to the illicit market include codeine and oxycodone (including formulations in combination with acetaminophen or ASA), which are usually taken orally, and hydromorphone, which is often injected.

As noted above, forging prescriptions, or obtaining prescriptions under false pretences, can also be used to divert opioids for non-medical use. Physicians writing opioid prescriptions under false pretences, and physicians and other health professionals with access to clinic, hospital or pharmacy supplies, may also carry out diversion. A wide range of opioids are diverted for personal use, including various forms of meperidine and morphine, as well as over-the-counter preparations such as acetaminophen-codeine combinations.

In Canada, the most commonly used illicit opioid is heroin. It is injected intravenously (the most common route of administration), "snorted" (taken intranasally), smoked or "chased" (vaporized). When being prepared for injection, heroin is commonly dissolved in small quantities of citrus juice or water. Chasing involves melting heroin and inhaling the fumes. The onset of effect with chasing is as rapid as with intravenous injection. Control over the dose through gradual incremental intake is most difficult with injecting and easiest with chasing. Injecting is the best way to avoid wasting any part of the available drug.

Opioids like heroin, prepared specifically for non-medical use, have highly variable and unpredictable purity. The purity varies over time and from place to place. Cases of accidental overdose are often attributed to this variation. Although relatively rare, unsafe fillers and additives have also been associated with serious adverse effects.

Users

Impoverished opioid users injecting opioids obtained from drug dealers are among the most marginalized patients seen by a physician. While such opioid users are commonly regarded as social deviants deserving punishment, other opioid users may be regarded with more compassion. For example, well-off health professionals diverting opioids for their own use may be regarded as victims of stress and as deserving of treatment. The marginalization of most opioid users makes this group difficult to serve.

Trends in Use

The results of a recent large survey indicate that at least 1.1 per cent (1.7 per cent of men; 0.6 per cent of women) of the U.S. population have ever used heroin within their lifetime. About 40 per cent of those who have used heroin have at one time been dependent on it. About 20 per cent of those who have used heroin (0.2 per cent of the population) are currently dependent on it. These survey results underestimate the actual figures, as the survey methodology excluded the homeless and the incarcerated (Epstein & Gfroer, 1997). Figures for Ontario are expected to be similar.

Trends in heroin use in North America in the 1990s include a dramatic drop in the age when heroin is first used, an increase in intranasal use and inhalation (Epstei & Gfroer, 1997), and higher levels of use (more frequent use and/or use in higher doses). These trends are the consequence of higher purity, lower prices and wider availability.

Psychoactive Effects of Opioids

While certain psychoactive effects are desirable when opioids are used medically in treating severe pain (see above), the commonest use of opioids for their psychoactive effects is in a non-medical context. In the literature, these psychoactive effects are usually summed up by the term "euphoria."

The "euphoria" associated with opioids has been described in the literature (Jaffe et al., 1997, McKim, 1997, Kalant, 1998, Gold, 1998, Reisine & Pasternak, 1996) as follows:

a) **The "rush" (associated with injecting or "chasing" fast-acting opioids such as heroin) is described as:**
   - intense, visceral sensation of warmth and thrill
   - high and intense pleasure (rush) compared to sexual orgasm
   - an intense sense of well-being.

b) **The high is described as:**
- foggy, unreal feeling of being detached from things
- pleasant, relaxed, dreamy state
- sleepy, trance-like state
- overwhelming sense of indifference to physical or psychic pain
- relaxing, anxiolytic
- sense of tranquillity and decreased apprehension
- elevation of mood and increased sense of self-esteem
- decreased concern with anticipated problems.

The four stages of injecting or chasing fast-acting opioids such as heroin can also be described as follows (Grund, 1993):

1. **the "rush"** — intensity varies with dose and tolerance
2. **the "high"** — duration and intensity vary with dose and tolerance; higher dose relative to tolerance required to achieve a state of unawareness referred to as being on the nod
3. **feeling "straight"** — not high, not on the nod and not sick
4. **feeling "sick"** — experiencing withdrawal.

When heroin is injected intravenously or chased, the "rush" (peak effect) is experienced within a minute or two and lasts a few minutes. The "high" may last up to an hour. Over time, tolerance develops to these effects. Fast-acting opioids like heroin have elimination half-lives of two to three hours. The elimination half-life is the time it takes for the concentration of drug in the blood to fall by half and may be one component determining the duration of the drug's effect. A regular heroin user generally starts feeling "sick" after four to six hours. Most of the four to six hours before the user begins feeling sick are spent in the "straight" phase.

In contrast with the marked psychoactive effects associated with injecting fast-acting illicit opioids, the effects associated with the medical use of oral slow-acting opioids (e.g., methadone used in the treatment of Opioid Dependence) are minimal. A "rush" is not experienced; it takes about two to four hours for plasma methadone concentrations to peak. Psychoactive effects reported with methadone are very mild and virtually disappear once the optimal maintenance dose has been established (i.e., once dose increases have stopped), stable plasma methadone levels have been achieved and tolerance to these effects has developed.

It should be noted that the term "euphoria," defined as "a feeling of well-being," is an imprecise term having very different meanings in relation to different drugs. For example, the relaxing euphoria produced by opioids is very different

from the sense of energy, power and exhilaration produced by amphetamines and cocaine (Kalant, 1998).

Opioid Tolerance and Cross-Tolerance

Regular administration/use of opioids leads to the development of tolerance to some of their effects. When individuals become tolerant to certain effects (e.g., to the psychoactive effects of fast-acting opioids), they require increasingly larger doses to achieve those same effects. Tolerance to some of the effects of a specific opioid commonly develops to a greater degree and more quickly than does tolerance to its other effects. For example, tolerance to the pupillary constriction caused by heroin develops much more slowly than tolerance to the psychoactive effects. Tolerance reflects the body's adaptation to the actions of the opioid — a protective counteracting of drug effects. While opioid tolerance is largely physical, setting, conditioning and learned compensatory behaviour also determine tolerance.

Related to the tolerance that develops with regular use of opioids is cross-tolerance, which refers to the ability of one opioid to produce tolerance to the effects of another opioid. Cross-tolerance explains why an individual stabilized on MMT will experience very little effect from a dose of heroin that previously produced significant effects. In summary, tolerance can *contribute* to the development of Substance Dependence, it can be a *consequence* of Substance Dependence, and it can also be a *characteristic* of Substance Dependence.

Physical Dependence and Withdrawal

Physical dependence on opioids is manifested by withdrawal when opioids are used regularly and then the amount used is significantly decreased or the opioid is discontinued abruptly. Withdrawal, like tolerance, reflects the body's adaptation to the action of the opioid. When regular administration/use of an opioid is significantly reduced or stopped, the body, which has to some extent adapted to its presence, cannot re-adapt quickly enough to its absence. The body's adaptation then becomes evident, expressed as withdrawal signs and symptoms that are in part "drug-opposite." For these reasons, withdrawal is more severe when higher doses have been used, the use has been over a longer period of time or the drug is discontinued more abruptly. Physical dependence can *contribute* to the development of Substance Dependence, it can be a *consequence* of Substance Dependence, and it can also be a *characteristic* of Substance Dependence.

Opioid Withdrawal Management (Detoxification)

Withdrawal management is commonly called detoxification, an older term that likens the substance to a toxin whose effects include physical dependence. At one time, it was believed that the primary cause of Substance Dependence was a fear of withdrawal, which could be cured by clearing the substance from the body. The focus was thus on the substance as the cause of dependence. It has since become obvious that relatively severe Substance Dependence can develop even when the objective signs of withdrawal are much less severe than those associated with opioids. When opioid dependence was seen as a moral failing, experiencing withdrawal was presumably viewed as having a punitive benefit. While opioid withdrawal management still has a place (including its place as the treatment for babies born to women using opioids or to women in MMT), it is now recognized that it is not a cure for opioid dependence. Nevertheless, opioid users may request assistance with detoxification either as a first step to recovery from their dependence or as a way of easing withdrawal when they are unable to obtain opioids. Opioid users may also attempt detoxification because they mistakenly believe it to be the only "real cure" for opioid dependence.

Detoxification from psychoactive substances, including opioids, can be undertaken with or without the support of health care professionals. When support is sought, opioid withdrawal can be managed either by a non-medical social support approach (not involving medication) or with the additional support of medications. In non-medical opioid withdrawal management, patients receive emotional and other support as they "kick the habit" or go "cold turkey." Non-medical opioid withdrawal management is contraindicated for pregnant women (because of the risks of spontaneous abortion or premature labour), for babies born to women tolerant to opioids, and for individuals with serious medical conditions (such as AIDS) that can be worsened by the physical stress. While it is not life-threatening for non-pregnant patients in MMT to undergo non-medical withdrawal, there is a very high risk of relapse. Continued maintenance or gradual tapering of methadone are clinically superior approaches.

Medically assisted opioid withdrawal management involves supportive care and the administration of medication. Options include the administration of clonidine and other medications for symptom relief, or the administration and subsequent tapering of opioids such as methadone as a temporary substitute for the opioid being discontinued. Medically assisted withdrawal management is generally contraindicated for pregnant women. In the experimental procedure known as "rapid opioid detoxification," the early stage of withdrawal is shortened and the severity increased by administering naltrexone to heavily sedated or anesthetized patients.

At present, there is no clear evidence supporting the superiority of a particular regimen of medication in managing opioid withdrawal. While medical withdrawal management eases opioid withdrawal by relieving some of its early signs and symptoms, some opioid-dependent individuals experience protracted withdrawal symptoms that persist for months. Without long-term treatment for opioid dependence, the rate of relapse to illicit opioid use following detoxification, whether medical or non-medical in approach, is very high.

For a variety of reasons, patients receiving methadone may wish to discontinue it or may be denied access to their medication. The recommended approach in cases of voluntary cessation of methadone is to gradually taper the dose in the context of ongoing care. In situations where access to medication is being denied, such as when patients are hospitalized or incarcerated (though medical staff should avoid this possibility), health care professionals must carefully assess the advantages and disadvantages of withholding care. Consideration should include the high risk of relapse to injection drug use, and the risks to pregnant patients or those with serious medical conditions (e.g., AIDS) that can be worsened by physical and emotional stress.

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chapter

2

Overview of Methadone Maintenance Treatment

John Brands, MHSc
Bruna Brands, PhD
and David Marsh, MD

OVERVIEW OF METHADONE MAINTENANCE TREATMENT

This chapter focuses on methadone maintenance treatment (MMT) and ends with a summary of the progress that has recently been made in meeting the need for MMT in Ontario.

The Rationale for Methadone Maintenance Treatment

Methadone is a long-term substitute for the opioid on which the patient was dependent. Other long-term opioid substitutes, such as heroin and LAAM (levo-alpha-acetylmethadol), are prescribed in other jurisdictions. In Canada, LAAM and buprenorphine have been prescribed under the Special Access program.

MMT involves the prescribing of methadone as part of a comprehensive program that includes counselling aimed at helping the patient reduce or stop harmful use of opioids and other psychoactive drugs (often including nicotine and alcohol). Case management and other medical and psychosocial services are also provided, either directly or by referral.

The Potential Benefits of Methadone Maintenance Treatment

MMT has the following *potential* benefits:

- Methadone is pure (free of unsafe fillers, additives and solvents), and the opioid content (dose) is known; it can help patients avoid the harmful consequences (e.g., phlebitis, overdose) of injecting illicit opioids of unknown purity.

- Methadone is legal; it can help patients avoid the harmful consequences (e.g., arrest, incarceration) of possessing illicit opioids.
- Methadone is dispensed in pharmacies; it can help patients avoid the harmful consequences (e.g., violence) of associating with drug dealers.
- Methadone is relatively affordable; it can help patients without conventional sources of relatively high income avoid the harmful consequences (e.g., arrest, incarceration) of engaging in illegal activity in order to generate the incomes required to buy illicit opioids. Patients may have generated such incomes through theft, burglary and drug dealing.
- It can put marginalized individuals in regular contact with the health care and social service systems, and can give treatment providers regular opportunities to provide individuals with medical, counselling and case management services they would otherwise not utilize. In general, opioid users are at a higher-than-average risk of suffering injuries and of acquiring infectious and other diseases (see below). The co-existence of psychiatric disorders (see below) is also common among opioid users, as are histories of physical, emotional and sexual abuse.
- Methadone can make it possible for patients to care for family members, to attend school and to engage in a greater variety of work.
- Substituting methadone (taken orally) for heroin (usually injected) can help patients to reduce or to stop injecting opioids, and to thereby avoid infectious blood-borne diseases (HIV infection, viral hepatitis) acquired by sharing needles.
- Methadone can help patients without conventional sources of relatively high income to avoid the harmful consequences (e.g., physical, emotional and sexual abuse; and in Canada, arrest for "communicating") of generating income in the sex trade, in which workers often have none of the protection society provides to other workers. It can also help patients who choose to work in the sex trade to avoid the harmful consequences (e.g., sexually transmitted diseases, unwanted pregnancy) of working while intoxicated.
- Substituting methadone (slow onset and long-acting) for heroin (fast onset and short-acting) can help to normalize neuroendocrine function (e.g., by restoring normal menstrual periods in heroin users). It can also help to normalize physical/psychological functioning through the day by alleviating the repeated cycles of intoxication and withdrawal experienced by heroin users. This normalization of neuroendocrine and physical/psychological functioning is particularly important for pregnant heroin users; heroin withdrawal can result in spontaneous abortion and premature labour, and developing babies share the stress of the ups and downs that characterize heroin use. This normalization is also important for patients suffering from other illnesses (e.g., AIDS), which this stress can worsen.

In benefiting the patient in the ways described above, methadone also benefits the patient's family and community in a variety of ways. It can reduce the costs to the community of policing, courts, prisons, health care, social services and support for the unemployed. More specifically, it can reduce the spread of infectious blood-borne diseases to the broader community by helping patients to avoid them (thereby reducing their sexual transmission) and by helping patients already infected to reduce or to stop injecting (thereby reducing the spread of disease through needle sharing). Methadone can also reduce the spread of sexually transmitted diseases in the broader community by helping patients working in the sex trade to avoid working while intoxicated.

It should be noted that methadone is pharmacologically effective only in opioid dependence. It has no pharmacological effect in dependence on other substances such as nicotine, alcohol, benzodiazepines or cocaine. Nevertheless, use and abuse of other substances, as well as dependence on other substances, may be identified in individuals with Opioid Dependence during the course of MMT and can be addressed through the medical, counselling and case management services offered in the course of MMT. Research has demonstrated the effectiveness of comprehensive MMT in reducing the harmful use of other substances (Preston, 1996).

The Potential Disadvantages of Methadone Maintenance Treatment

The disadvantages of regularly taking methadone (compared with abstinence from all opioids, including methadone) are as follows:

- Patients may experience side-effects from methadone. Common and persistent side-effects include sweating and constipation.
- Patients become dependent on their methadone prescriber. A patient in MMT is physically dependent on a substance (methadone), and his or her prescriber controls the access to it. The power imbalance gives the methadone-prescribing physician a great deal of control that can be misused.
- Patients may be discriminated against. MMT patients may be stigmatized as "still addicted" by the broader community and by patients in abstinence-based addiction treatment programs or participants in mutual help groups. Other health and social service professionals (including addiction treatment providers) who do not understand MMT, and whose experience has been limited to abstinence-based addiction treatment, may also discriminate against MMT patients. MMT patients may also encounter discrimination in obtaining and retaining employment, and in accessing public and private services.

- Patients commonly find certain practices carried out by some programs or clinics degrading and demeaning. An example is the practice of an attendant observing patients voiding urine for drug screening.
- MMT can be inconvenient for patients. A number of factors impede patient mobility. These include the onset of opioid withdrawal and the emergence of opioid craving in patients who abruptly stop taking methadone; requirements for regular visits to the physician, counsellor and pharmacist; the limited number of programs and physicians currently offering MMT in many parts of Ontario; and the limited number of pharmacies currently stocking methadone. Other inconveniences include attending the pharmacy for observed ingestion or for picking up take-home methadone (much more of an inconvenience with methadone than with other medications); keeping the methadone at hand and safe, and taking it daily at the same time; attending the lab on short notice to provide random urine samples; and attending the pharmacy at short notice for random take-home callback (see Chapter 8).
- Patients may be exposed to negative influences when attending programs. When MMT is provided in the context of a dedicated program where patients are concentrated, they may come into regular contact with others still using opioids, alcohol and other drugs. This is less likely when MMT patients are integrated into the general practices of community physicians, where drug users are less concentrated.
- Methadone is an ongoing expense for patients. Although it is far less expensive than the illicit opioids (e.g., heroin) that it replaces, there is still a direct cost to patients without insurance.

Alternative Treatments for Opioid Dependence

Occasionally, individuals are able to recover from opioid dependence through self-help or by "maturing out," or "growing out," of it. Given the serious nature of opioid dependence and its consequences for the dependent person and for society (see above) this approach alone cannot be relied on. For some opioid-dependent individuals, mutual help groups (e.g., Narcotics Anonymous), outpatient "drug-free" counselling, and long- or short-term residential "drug-free" treatment are effective. However, for most opioid-dependent individuals, each of these approaches alone is not as effective as comprehensive MMT alone. In other jurisdictions, opioid substitutes other than methadone (e.g., LAAM, buprenorphine, heroin) are used as maintenance medication in the way methadone is used in Ontario; these are not currently approved for use in Canada.

Another alternative is long-term treatment with naltrexone, a drug that blocks the effects of opioids and does not have any opioid effects. Naltrexone, an opioid antagonist, has similar actions to naloxone (Narcan®) but may be taken orally and has a substantially longer elimination half-life. Naltrexone is started after opioids have been discontinued for at least 10 days. In a patient taking naltrexone regularly, opioids will have no effect; this will presumably stop a patient from self-administering opioids. While there have been excellent results in highly motivated (or highly coerced) patient groups, overall compliance and retention in treatment is poor. Naltrexone also has a tendency to produce or enhance depression and very effectively blocks the effect of opioid analgesics, thus making it more difficult to manage patients with moderate to severe pain (see Chapter 1).

The Effectiveness of Methadone Maintenance Treatment

In a comprehensive review of research on MMT, the U.S. Department of Health and Human Services describes the effectiveness of MMT as follows:

The use of methadone in treating opioid dependence began with research in the United States during the early 1960s. It was shown that individuals addicted to heroin could be successfully engaged in treatment when prescribed methadone to relieve opioid withdrawal and reduce opioid craving. Over thirty years of research have demonstrated the effectiveness of using methadone in treating heroin addiction when measured by:

- reductions in the use of illicit drugs;
- reductions in criminal activity;
- improvements in social health and productivity;
- improvements in general health;
- retention in addiction treatment; and
- reductions in needle sharing and HIV infection.

It should be noted that adverse social conditions (e.g., high levels of systemic poverty, homelessness and unemployment) may severely constrain the effectiveness of MMT in reducing dependence on social assistance, and in reducing income-generating activities such as property crime and drug dealing by facilitating conventional employment (U.S. Department of Health and Human Services, 1995).

The Components of Methadone Maintenance Treatment

The following description of treatment components reflects:

- the requirements of the *Methadone Maintenance Guidelines* (included with this Guide), which are endorsed by the College of Physicians and Surgeons of Ontario (CPSO), the Centre for Addiction and Mental Health (CAMH) and the Ontario College of Pharmacists (OCP)
- the clinical practices described in *Methadone Maintenance: A Physician's Guide to Treatment* (Brands & Brands, 1998), available from CAMH
- current clinical practice in Ontario insofar as it is provided in accordance with the *Methadone Maintenance Guidelines*.

The Treatment Team

The treatment team consists of the physician, the pharmacist and the counsellor/therapist/case manager. Patients who receive their MMT from general practitioners in the community (in solo or group practice) may receive counselling and case management from the prescribing physicians. Alternatively, patients may receive these services by referral to community agencies offering addiction counselling services. Patients who receive their MMT through specialized programs may receive counselling from counsellors working on-site. Counselling is an essential component of MMT. Other ancillary services (e.g., assistance with housing, assistance with employment) may be provided as well, either on-site or by referral.

In specialized programs, physicians commonly work closely with on-site counsellors. A cohesive treatment team, which may include an on-site pharmacist and/or a nurse, makes therapeutic decisions. In other situations, MMT involves pharmacists and counsellors working in the community. In all these situations, good communication among everyone involved is essential to providing safe and effective MMT.

Informed Consent to Treatment

Before beginning MMT, the physician, pharmacist or counsellor informs the patient about the adverse effects of methadone (see Chapter 3). The likelihood of withdrawal if the methadone dose is reduced or if methadone is discontinued, the long-term nature of MMT, the disadvantages of MMT (see above) and the alternatives to MMT (see above) must each be discussed. The patient is then asked to consider formally consenting to MMT, which cannot begin until consent is provided.

Consent to Sharing Patient Treatment Information

At the start of MMT the patient is asked to consent to having his or her medical records made available to the CPSO. Certain information (e.g., the patient's name and health card number, the name of the patient's physician and the date MMT started) is entered into a database maintained by the CPSO (see below); the CPSO may review other medical information in the course of CPSO audits of the patient's physician (see below).

As required, the patient is also asked to consent to having treatment information provided to other third parties. With a few exceptions (where sharing of information is required by law, e.g., in Ontario, the sharing of certain information with child protection agencies), patient treatment information is confidential and individual treatment providers cannot share such information with anyone else without prior consent of the patient. However, in some circumstances it is necessary to share this information, such as when a patient is hospitalized or incarcerated, in order to maintain the continuity of treatment.

Medical Assessment

The determination of an individual's suitability for MMT is crucial. To be considered for MMT in Ontario, the patient must meet the following criteria:

- An individual must meet the diagnostic criteria for Opioid Dependence as defined in the DSM-IV.
- An individual should be 18 years of age or older.
- There should be evidence of extensive past opioid use and/or failed treatment attempts. **Previous unsuccessful methadone treatment should not exclude a patient from methadone treatment.**
- There should be at least one urine drug screen positive for opioids prior to initiating methadone treatment.

Occasional users of opioids are not eligible for MMT, even if they meet DSM-IV criteria for *Opioid Abuse* (see Chapter 1).

Pregnancy and HIV infection are also identified in the course of the medical assessment. Where treatment places are limited, eligible pregnant opioid users and eligible opioid users with HIV infection may receive priority over other potential patients.

Other medical conditions associated with drug dependence, drug injecting and the lifestyle associated with drug dependence (particularly the lifestyle of users without

conventional sources of higher income) are also identified in the course of the medical assessment. These conditions include poor nutrition, dental problems, cirrhosis and infectious diseases such as phlebitis, endocarditis, hepatitis B and C, HIV infection, sexually transmitted diseases and tuberculosis. Other health-related issues (e.g., preventing unwanted pregnancy) are also addressed. Psychiatric problems, such as depression, personality disorders, anxiety disorders and post-traumatic stress disorder, are also identified.

Use, abuse and dependence (see Chapter 1) involving other substances (e.g., nicotine, alcohol, benzodiazepines, cocaine) are also identified in the course of the medical assessment.

The physician makes the diagnosis of Opioid Dependence in the context of the medical assessment. Although the physician may rely on the assistance of the counsellor in determining suitability for MMT, the determination of suitability for MMT is the physician's responsibility because it is the physician who will be prescribing methadone.

Treatment Agreement

Before methadone is prescribed, the physician or treatment team enters into a treatment agreement with the patient. Such an agreement outlines their respective obligations. This begins the ongoing process of orienting and re-orienting the patient to the policies and procedures involving the physician, counsellor and pharmacist.

Psychosocial Assessment and Treatment Plan

A comprehensive psychosocial assessment, utilizing an instrument such as the Addiction Severity Index, is conducted as soon as possible after the medical assessment and, if possible (and applicable), before methadone is prescribed. The physician or treatment team, in collaboration with the patient, draw up a comprehensive treatment plan, outlining treatment objectives/expectations. The psychosocial assessment is repeated periodically throughout the course of treatment, and the treatment plan is modified as necessary.

Counselling and Case Management

Research has demonstrated that the effectiveness of MMT is enhanced if the patient engages in counselling. It is essential that psychosocial issues be addressed in the course of MMT. Psychiatric disorders may contribute to and/or result from opioid dependence, and histories of physical, emotional and sexual abuse are not uncommon among MMT patients. Use, abuse and dependence (see Chapter 1) involving other substances (e.g., nicotine, alcohol, benzodiazepines, cocaine) are

common among MMT patients and can in part be addressed through counselling. Many patients also benefit from assistance with housing, employment, etc. The prescribing physician, another physician (e.g., a psychiatrist) or a non-physician counsellor may provide counselling and case management.

General Medical Services

Provision of general medical services is essential in addressing any physical complications of substance use identified during the medical assessment. The physician ensures that the patient is aware of any conditions detected and provides care or referral as appropriate. Some conditions detected in the course of the medical assessment (e.g., pregnancy, HIV infection, viral hepatitis, dependence on other substances) may require referral to a specialist.

Dispensing and Take-Home Doses

Methadone is ideally taken once a day at approximately the same time every day. The pharmacist prepares it in individual doses (for more detail, see later chapters). Methadone is ingested under the observation of the pharmacist or another health care professional, except when the physician prescribes take-home doses. As the patient becomes more stable, he or she is provided with a limited supply of methadone to take home. The number of take-home doses that the patient receives depends on the patient's time in treatment and the patient's stability at the time. The number is specified by the physician on the prescription. The physician or treatment team determine a patient's stability by assessing program participation (including adherence to the treatment agreement), cognitive stability (including appropriate use and safekeeping of take-home medication), reduced and/or less harmful drug use or abstinence from drugs (as determined through history, physical examination and urine toxicology screening), and social health.

In Ontario, take-home methadone is not provided during the first three months of MMT. Not providing take-home methadone during the first three months gives the physician the opportunity to ensure that the methadone dose is adequate (so the patient is no longer experiencing withdrawal) and not excessive (so the patient is not becoming intoxicated) before he or she receives take-home methadone. It also gives the physician or treatment team the opportunity to ensure that the patient has achieved sufficient stability.

The patient generally receives more take-home doses as he or she progresses in treatment. In Ontario, routine take-home methadone does not exceed a six-day supply (i.e., six bottles), which, for example, a stable patient might receive after achieving 12 months of abstinence from substances of abuse. Under special

circumstances (e.g., a patient working or vacationing in areas of Ontario where methadone is not available, or visiting jurisdictions where methadone is not available but can legally be possessed), a patient may be provided with more than a six-day supply, typically to a maximum 14-day supply.

The *Methadone Maintenance Guidelines* include criteria (based on patient stability) and a schedule for providing take-home methadone. A patient who is given take-home methadone enters into a take-home agreement with the physician or treatment team. Such an agreement outlines the patient's responsibilities, including appropriate use and safekeeping of the methadone. When quantitative methadone analysis is available, the take-home agreement includes a (random) callback provision, whereby the patient agrees, if requested, to come to the pharmacy on short notice to exchange the unused medication for freshly prepared medication and to return the empty medication bottles.

A patient receiving take-home methadone (including one receiving six days' take-home medication) periodically has the effect of an observed dose assessed by the physician or pharmacist, with attention to signs of intoxication. This can be accomplished by carrying out an assessment an hour or two after the observed dose is ingested, or by having the patient attend for observed dosing two days in a row.

Should a patient receiving take-home methadone become significantly less stable, the number of take-home doses might be reduced or take-home doses might be discontinued. Re-evaluation of take-home doses is also considered if the patient is found to have tampered with the urine toxicology screening (e.g., has provided a urine sample that was not fresh or that was obtained from someone else). Take-home doses are discontinued, and the prescribed dose reassessed, if the patient is found to have been diverting part of his or her methadone (see below).

Urine Screening

A key component of MMT is urine toxicology screening for the methadone metabolite EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrolidine) (see Chapter 3), other opioids and other drugs of abuse, such as benzodiazepines and cocaine. This is done for a number of reasons. As part of the medical assessment, a urine screen may help in diagnosing opioid dependence. As a routine component of treatment, a urine screen can confirm a patient's reported drug use and thereby help inform treatment decisions. For a patient receiving take-home methadone, a urine screen can help confirm that the patient is taking the medication.

The patient's time in treatment and stability at the time determine the frequency of urine screening (conducted randomly). Sample criteria for scheduling urine screening are included in the *Methadone Maintenance Guidelines*. Voiding of urine for screening is supervised; many programs and physicians require that voiding take place under observation.

Some programs and physicians ask patients to prove to the pharmacist, before receiving their methadone, that they have provided required urine samples. Patients do this by presenting to the pharmacist a slip or a card signed by the person supervising the urine collection.

Patient Transfer

In certain situations, patients may be transferred to another physician or treatment team or to another pharmacy.

The physician or treatment team may occasionally find it necessary to discharge a patient from their care against the patient's wishes. This generally happens when there has been a serious breakdown in the working alliance between the patient and the physician or treatment team. This might, for example, result from a serious breach of the treatment agreement by the patient (e.g., intimidating/threatening or assaulting a member of the treatment team or another patient). In such situations the physician or treatment team may be unable to ensure the safety of other patients and staff while continuing to treat this patient. If a patient is discharged from the care of the program/physician, the patient is transferred to another program/physician that is able to continue the patient's MMT without interruption.

Likewise, the pharmacist may occasionally find it necessary to discontinue providing pharmacy services to a patient against the patient's wishes. This generally happens when the patient has broken the agreement between the patient and the pharmacy. Such a breach may, for example, involve disruptive behaviour or shoplifting. If pharmacy services for a patient are discontinued, the patient is referred to another pharmacy (see Chapter 12).

Patient Hospitalization or Incarceration

It is essential that patients continue to receive their maintenance dose of methadone when they are hospitalized, when they utilize inpatient withdrawal management services (e.g., for "detoxification" from other drugs such as cocaine), or when they are incarcerated. Good communication among all those involved, including hospital or

prison staff and the patient's community treatment team, is essential to ensure that the patient does not miss any doses and does not receive overlapping prescriptions (see Chapter 9).

Discontinuation of Methadone Maintenance Treatment

The achievement of treatment objectives and the patient's wishes determine the length of time that a patient remains in MMT. A patient may remain in MMT for years or even decades. Occasionally, the physician or treatment team may decide to stop providing MMT to a patient because it is not benefiting the patient. Generally, a patient not picking up many, or most, doses indicates a lack of benefit. Alternatively, a patient may decide to stop taking methadone at any time. If methadone is discontinued under either of these circumstances, it is generally discontinued gradually (tapered) so as to minimize withdrawal. Only in exceptional circumstances (e.g., emergencies, situations where methadone has become contraindicated) should a patient's methadone dose be abruptly reduced or discontinued against his or her wishes (see Chapter 6).

The Treatment of Pain in the Context of Illicit Opioid Use and Methadone Maintenance Treatment

Many individuals dependent on illicit opioids (particularly individuals with lower incomes) are at a higher-than-average risk of suffering trauma from violence, arrest and incarceration, etc. associated with their lifestyle. These individuals, and patients in the early stages of MMT, are also at a higher-than-average risk of suffering serious illness. Furthermore, individuals dependent on illicit opioids suffer accidents (e.g., motor vehicle accidents) like the rest of the population. Undertreatment of pain is common when these individuals seek medical attention for painful conditions or when they undergo surgery. Undertreatment of pain involving such individuals can lead to disruptive behaviour by frightened or angry patients and to discharge against medical advice. Conventional opioid pain relievers are appropriate when such individuals experience severe acute pain. To ensure adequate opioid dosing, it should be noted that such individuals might have developed considerable tolerance to the analgesic effects of opioids. Therefore, while on methadone patients should be started on usual doses of analgesics but receive frequent reassessments as they may require higher and/or more frequent doses (see Chapter 12).

The Regulation of Methadone Maintenance Treatment in Ontario

In Canada, MMT is controlled at various levels through statutes, regulations, self-regulation, administrative procedures and guidelines. The objective of this control is to ensure safe and effective individual patient care, and to protect the public from the very few physicians, pharmacists and patients who unethically or illegally profit from prescribing, dispensing or diverting methadone. The end result of poor clinical practices, and unethical or illegal practices, can be accidental overdose involving individuals not in MMT.

In Canada, the prescribing of methadone is subject to more regulation than the prescribing of most other drugs. First, the prescribing of methadone is subject to the same laws governing the prescribing of other opioids, such as morphine. Second, physicians are required under federal regulation to obtain special authorizations before prescribing methadone. The Office of Controlled Substances grants these authorizations.

In Ontario, the CPSO is responsible for ensuring the quality of care provided by methadone-prescribing physicians. This is accomplished by various means. First, the CPSO determines the education, training and other qualifications that Ontario physicians must have to become authorized to prescribe methadone for opioid dependence. These qualifications include structured, academically centred training. Second, the CPSO acts on complaints about methadone-prescribing physicians. Third, the CPSO carries out peer-based audits of the practices of methadone prescribers for the purpose of quality improvement. Adherence to the *Methadone Maintenance Guidelines* and compliance with the college's reporting requirements are monitored in the course of the audits. The CPSO also monitors methadone prescribing and identifies potential prescribing problems through its database of Ontario methadone prescribers and recipients. The CPSO shares prescriber information with the Ontario College of Pharmacists (OCP).

Much useful information to guide MMT in Ontario has emerged from a recent series of CPSO-sponsored audits of the practices of Ontario methadone prescribers. Where there were problems, they most commonly involved insufficient diagnosis and assessment of new patients. Such problems include starting patients on doses higher than those recommended in the *Methadone Maintenance Guidelines* (the "Guidelines"), increasing patients' doses more quickly than recommended in the Guidelines and providing patients with take-home methadone sooner than recommended in the Guidelines (see "Medical Assessment," "Psychosocial

Assessment" and "Dispensing and Take-Home Doses" under "The Components of Methadone Maintenance Treatment" above).

Other information to guide the prescribing of methadone in Ontario has come from the Chief Coroner for Ontario. In an ongoing review of methadone-related deaths in Ontario, the Coroner has determined that the annual number of deceased in whom methadone was detected has been consistently increasing from 1996 to 1998. In 1997, for example, there were 47 methadone-related deaths across Ontario. Of these 47 deaths, in seven (15 per cent) methadone alone was the cause of death; in 29 (about 60 per cent) it was a contributing factor; in the rest the presence of methadone was incidental. About 60 per cent of the total of the 47 methadone-related deaths in 1997 were of individuals not in MMT. Patients who died while in MMT had been in treatment an average of three to eight days. The majority of the 47 deceased had ingested one or more other drugs (e.g., alcohol, diazepam, codeine and cocaine) in addition to methadone. In light of these findings, the coroner has suggested that deaths of patients in MMT might be reduced by starting patients on a low dose and increasing the dose slowly, as recommended in the *Methadone Maintenance Guidelines* (J. Cairns, personal communication, February 12, 1999).

The Centre for Addiction and Mental Health (CAMH) presently offers education and training of physicians, pharmacists and counsellors interested in providing MMT. The Centre also has a leading role in the ongoing development of clinical guidelines, other reference materials, and training/educational materials for physicians, counsellors and pharmacists involved in MMT (e.g., *Methadone Maintenance: A Physician's Guide to Treatment* [Brands & Brands, 1998], the first guide in this series).

In some jurisdictions methadone is even more highly controlled than in Ontario. In many U.S. states, for example, only full-service programs subject to detailed federal, state and municipal regulations can provide addiction treatment involving methadone. In other jurisdictions (e.g., Belgium), methadone may be prescribed like other prescription opioids by any physician.

Methadone Diversion

Patients receiving take-home methadone have been reported to, on occasion, divert part of their medication to opioid users in opioid withdrawal, to opioid users without access to MMT, to opioid users wanting to try "home detox," to individuals wanting to ameliorate unwanted effects of other drugs (e.g., cocaine) or to individuals wanting to use it for the psychoactive effects that may be experienced at

higher doses relative to tolerance. Much of the diversion that occurs is to family and friends. Patients diverting for income may be supplementing low incomes and/or using the proceeds to buy illicit opioids or other drugs. The prevailing reasons for diversion can be expected to vary over time and from place to place with (among other things) the prevailing availability and nature of MMT. While methadone may not be an opioid of choice on the illicit market, especially when others are available (see below), there has always been a market for diverted methadone.

There are a variety of safeguards against methadone diversion. In Ontario, the CPSO uses its methadone prescriber/recipient database to help prescribers ensure that patients do not receive methadone prescriptions from more than one physician at a time. Methadone is dispensed directly to the patient, who (if not known by the pharmacist) is required to present identification before receiving it.

The monitoring of the effects of observed doses during the three-month dose adjustment period helps ensure that the patient is taking his or her full methadone dose and that it is not excessive. A patient receiving take-home methadone also has the effect of an observed dose periodically assessed by the pharmacist or another member of the treatment team. This helps ensure that the patient is taking his or her full methadone dose; opioid intoxication in a patient following an observed dose to which the patient was previously tolerant may indicate diversion of a portion of earlier doses.

Urine screens that include testing for EDDP (2-ethylidene-1,5-dimethyl-3, 3-diphenylpyrolidine) help confirm that the patient is taking his or her take-home methadone. In addition callback of take-home methadone and empty bottles is another way of deterring and identifying diversion. Missing or diluted take-home methadone or missing empty bottles may indicate diversion of methadone and/or containers. Finally, the way methadone is dispensed (with each daily dose dissolved in 100 mL of fruit drink) makes it less attractive than most opioids on the illicit market. The large volume deters injection and makes it difficult to conceal. Because of its slow onset of action when taken orally, it is also not the opioid of choice when others are available. Nevertheless, methadone has a street value that results in a certain level of diversion.

If a patient receiving take-home methadone is found to be diverting part of his or her methadone, the patient stops receiving take-home methadone and is asked to attend the pharmacy daily for observed ingestion. The patient may also have his or her dosage reduced if it appears that he or she can manage on a lower dose.

(For a more detailed discussion of the steps pharmacists can take to minimize diversion, see Chapter 8).

Methadone Maintenance Treatment as a Harm Reduction Strategy

Dr. Perry Kendall, the former president and CEO of Ontario's Addiction Research Foundation* (ARF), defined harm reduction as "a pragmatic approach to substance use which attempts to decrease the consequences for individuals and society." Dr. Ernest Drucker, the author of a number of leading papers on the topic, characterizes harm reduction as a paradigm that "approaches illicit drug use and addiction not as a phenomenon caused by psychological and moral factors but rather as one causing extensive social problems and threatening public health."

The World Health Organization describes the rationale for harm reduction strategies as follows:

> Until recently, there has been little to challenge the approach to drug policies in which a "war" is being waged against illicit drugs. The focus has been on the substance with minimal attention paid to the well-being of the drug user and his or her family and community. Factors that significantly influence international drug policies often have little to do with health or social issues. It is recognized that it is no longer acceptable to ignore the impact drug policies have on the health and well-being of our communities. After decades of highly restrictive drug policies, it is evident that the international drug problem is still growing, to the greater harm of our communities. In response to this, drug policies are being questioned and there is a call for a more balanced approach between the control of substances and the prevention of the harm associated with them (World Health Organization, 1993).

Owing to a lack of a widely accepted definition, and because of its association with a range of controversial drug intervention strategies, the term *harm reduction* has been largely misunderstood. The term is currently used in two different ways — exclusively and inclusively.

The *exclusive* definition of "harm reduction" excludes strategies that reduce drug-related harm by reducing demand for drugs, such as effective treatment. It therefore groups together a range of drug intervention strategies, such as needle exchange, that

*The Addiction Research Foundation is now a division of the Centre for Addiction and Mental Health.

fall outside of supply and demand reduction but reduce harm for those who continue to use (World Health Organization, 1993).

The *inclusive* definition of "harm reduction" includes all strategies that reduce drug-related harm, whether or not drug use is reduced. This is how it is defined in this Guide. Harm reduction therefore includes the following:

1) **strategies that focus on reducing drug use**
   - strategies to reduce drug supply (e.g., restricting the availability of alcohol and nicotine, intercepting and destroying illicit drug shipments, imprisoning illicit drug dealers) *insofar as such strategies reduce harm*
   - strategies to reduce drug demand (e.g., treatment, education) *insofar as such strategies reduce harm*.

2) **strategies that focus on reducing the harm of drug use, including:**
   - reducing unsafe drug administration (e.g., supplying unused needles)
   - promoting less hazardous routes of administration (e.g., promoting a switch from drug injecting to smoking)
   - promoting the use of less harmful drugs (e.g., MMT)
   - creating a safer alcohol/drug-using environment (e.g., providing safe injection facilities)
   - modifying risky behaviour associated with drug use (e.g., promoting driving by a "designated driver," supplying condoms)
   - reducing discriminatory and persecutory practices against drug users (e.g., decriminalizing drug use).

When conflict arises, strategies that focus on reducing the harm of use should take precedence over those that focus on reducing use (World Health Organization, 1993). Both strategies are employed simultaneously in many jurisdictions, including Ontario. In many societies, including ours, the level of control required to completely eliminate drug use is socially unacceptable.

Physicians, counsellors and pharmacists involved in providing MMT generally support abstaining from harmful use of licit drugs, abstaining from illicit drugs and (ideally) discontinuing methadone as an ultimate goal for their patients. Nevertheless, recognizing the multiple and complex causes of Substance Dependence, the majority of these practitioners allow a considerable amount of time for abstinence to be achieved. They, too, are prepared to provide a variety of medical and psychosocial services during the time it takes for the patient to become abstinent. Sustained contact with the patient can be effectively maintained through the prescribing of methadone with its attendant requirements.

At times a distinction has been made between treatment that is oriented towards harm reduction and "abstinence-based" treatment. Abstinence-based treatment, in this context, is oriented to achieving almost immediate, complete and sustained abstinence from all (or almost all) psychoactive substances. This is, however, a false dichotomy, since patients in any form of treatment who achieve abstinence quickly and maintain it have reduced the harm of their drug use for themselves and others. Unfortunately, as outlined in Chapter 1, opioid-dependent patients who attempt detoxification frequently relapse to problematic drug use, and not all MMT patients are able to quickly achieve abstinence from all other drugs. The Ontario *Methadone Maintenance Guidelines* allow a broad range of treatment program formats, including those designed for patients who can achieve sustained abstinence and those for patients who need a more gradual process of change. MMT providers should ensure that their individual treatment approach does not increase harm when their patients are unable to quickly and permanently achieve total abstinence. Some opioid users seeking treatment prefer "abstinence-based" treatment. They want it either because they believe that it provides the only "real cure" or because they feel that they are weak or bad and therefore require or deserve uncompromising "tough" treatment. At times this may be an expression of underlying psychopathology.

The Availability of Methadone Maintenance Treatment

In the years leading up to 1996, the purity of heroin sold in Ontario had increased, its price had fallen, it had become more easily available, and there were indications that the number of individuals using it and dependent on it had increased. This trend was accompanied by only minimal improvements in the overall availability of MMT, a relatively inexpensive treatment of proven effectiveness that had been used as a treatment for opioid addiction for over 30 years. Specialized programs had more individuals on waiting lists than in treatment. This was unacceptable to users and to treatment providers advocating for the provision of effective treatment.

In 1995, user advocates argued persuasively and successfully that MMT needed to be expanded across Ontario, particularly in light of the potential for an AIDS epidemic among injecting opioid users. Other jurisdictions had already experienced such epidemics. In the summer of 1996, the Ontario Ministry of Health, the CPSO, the OCP and the Addiction Research Foundation (ARF) launched a joint effort to expand MMT while maintaining a high quality of care. The CPSO, OCP and ARF, in consultation with addiction treatment providers and user advocates, developed new guidelines for Ontario, the *Methadone Maintenance Guidelines*. These new guidelines are compatible with a wider variety of treatment approaches than previous guidelines and focus on accepting and retaining eligible opioid users

in MMT. They also provide far more detailed clinical guidance on the safe and effective provision of MMT than previous guidelines. ARF developed a training program with supporting reference materials (e.g., *Methadone Maintenance: A Physician's Guide to Treatment* [Brands & Brands, 1998]) suitable for community physicians. The new guidelines and training program facilitated the authorization of community physicians.

Since the summer of 1996, the number of Ontario physicians prescribing methadone, the number of patients in MMT across Ontario and the number of pharmacies dispensing methadone across Ontario have increased dramatically, particularly in the Greater Toronto Area. The number of Ontario physicians prescribing methadone for opioid addiction has almost tripled from 41 in July 1996 to 114 in March 1998. Many of the physicians new to providing MMT are doing so in the context of solo or group community practices. As the number of physicians providing MMT has grown, established programs (e.g., the ARF opiate clinic) have increased their caseloads under the new guidelines. Over a two-year period, from September 1996 to August 1998, patients were added to the total in MMT across Ontario at 10 times the rate they were added in 1994 and 1995. This resulted in an almost fourfold increase in the number of patients in MMT over this two-year period, from just over 1000 to just under 4000.

Despite the dramatic increase in the number of patients in MMT across Ontario — an increase that is consistent with a past, unmet, need — it has been suggested that the need for MMT in Ontario is still far in excess of the supply. A conservative estimate is that 10,000 Ontario opioid users would be eligible for MMT, twice the number in treatment at the end of August 1999. It should also be noted that the expansion of MMT outside the Greater Toronto Area has been much less dramatic. There are still many medium-sized municipalities in Ontario where MMT is not available, where availability cannot meet the need or, when there is only one provider, where the treatment approach is not acceptable to a wide range of users interested in treatment. Furthermore, the increase in the number of physicians providing MMT has not kept up with the increase in the number of patients in MMT. Consequently, many community physicians are carrying relatively high patient caseloads that include significant numbers of relatively complex cases. Finally, while methadone prescribing has increased dramatically overall, the availability of drug counselling, mental health care and other psychosocial services for patients in MMT have not kept up, so the full potential of MMT remains to be realized.

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chapter

Methadone

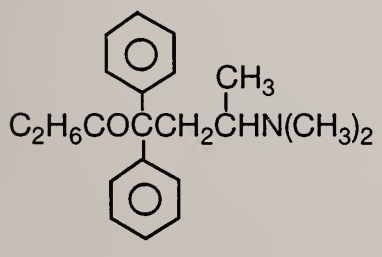
3

John Brands, MHSc
Bruna Brands, PhD
and David Marsh, MD

METHADONE

Methadone is an opioid, a drug with morphine-like effects. The opioid group of drugs includes opiates, semisynthetics and synthetics. Methadone, developed by IG Farbenindustrie in 1941, is one of the earliest synthetics. Methadone was originally named Hoechst 10820. After the Second World War, many companies used the formula, including Eli-Lilly in the United States, which marketed it as a pain reliever under the brand name Dolophine (probably from the Latin *dolor* [pain] and *fin* [end]) (Preston, 1996). In 1963, Drs. Vincent Dole and Marie Nyswander, working in New York, began testing daily doses of 80 to 120 mg/day as maintenance treatment for opioid dependence (Dole & Nyswander, 1976).

The Structure of Methadone



The Effects of Methadone and Other Opioids

Therapeutic Use of Opioids

Opioids are most commonly used medically (on the advice of a physician or pharmacist for recognized therapeutic indications) to relieve pain, cough or diarrhea. Opioids are also used in the treatment of Opioid Dependence to relieve opioid withdrawal and craving. In Canada, methadone is currently the only opioid approved for use in the long-term treatment of opioid dependence.

Like other opioids, methadone is an analgesic and is occasionally used for the relief of severe chronic pain (see Appendix 8). It is generally reserved for situations in which other opioid pain relievers (e.g., morphine) have proved ineffective. Methadone dosing for pain is different from methadone dosing for opioid dependence (see Appendix 8).

Whether a particular opioid effect is desirable or undesirable depends on whether it is being used therapeutically and on the indication. For example, for hospitalized patients receiving high doses of morphine for pain and for individuals using illicit heroin, the psychoactive effects — when experienced as "tranquillity and decreased apprehension" or as an "overwhelming sense of indifference to physical or psychic pain" (see "Psychoactive effects of opioids" in Chapter 1) — are desirable. Those effects are not pertinent when, for example, hydrocodone is used in treating cough (although, in this case, decreased apprehension may also be pertinent). Similarly, for patients receiving diphenoxylate for diarrhea, the constipating effect is desirable, whereas it is not desirable for patients receiving methadone for opioid dependence.

The Safety of Methadone

Compared with many other prescribed drugs, methadone is notable for its lack of long-term adverse effects. Studies of the long-term administration of methadone have confirmed that it is a medically safe drug. It has been demonstrated that the administration of methadone at doses of 80 to 120 mg per day is not toxic or dangerous to any organ system after continuous treatment for up to 14 years. When prescribed appropriately, methadone does not impair psychomotor performance (reaction time, attention span) or intellectual capacity. Methadone has also been used successfully in treating opioid-dependent pregnant women since the early 1970s; there is agreement that methadone can be safely administered during pregnancy with little risk to the mother and infant (U.S. Department of Health and Human Services, 1995).

Patients in methadone maintenance treatment (MMT), or users of diverted methadone, may accidentally overdose because of the slow onset of its effects. For non-tolerant adults, a single day's maintenance dose of methadone (50–100 mg) can be lethal (Harding-Pink, 1993). For those beginning MMT, starting doses of 40 mg have led to deaths after three days of treatment (Caplehorn, 1998). The lethal dose is less if it is taken together with other opioids, alcohol, benzodiazepines or barbiturates. Children may overdose if they mistakethe medication for a drink. A 10 to 20 mg dose of methadone can be fatal to a child (Aronow et al., 1972). There are a number of safeguards against accidental overdose included in dispensing practices (see Chapter 6).

Adverse Effects of Methadone

Methadone is generally well tolerated but does produce some adverse effects. Certain adverse effects of methadone often persist while most tend to subside over time. Some of the more persistent adverse effects of methadone (e.g., constipation) are treatable.

More common and often persistent adverse effects of methadone (Preston, 1996):

- sweating
- constipation
- changes in sexual desire and functioning
- insomnia.

Adverse effects of methadone that tend to subside over time (Preston, 1996):

- reduced appetite, weight gain
- nausea
- drowsiness
- tension, nervousness.

Some other less common adverse effects that have been reported with methadone:

- flushing
- vomiting
- dizziness, light-headedness, unsteadiness, faintness
- itching
- dry mouth
- dysphoria
- palpitations
- swelling of feet and ankles
- muscle and joint pain

- heaviness in arms and legs
- abdominal cramps.

Opioid Intoxication

When administered in doses in excess of therapeutic doses, opioids (including methadone) may cause intoxication characterized by:

- psychoactive effects (see Chapter 1)
- mild to moderate degree of sedation (e.g., drowsiness, sleepiness, "nodding").

Opioid Overdose

Opioid overdose (including methadone overdose) is a medical emergency. It is characterized by:

- severe degree of sedation (e.g., stupor, coma)
- marked respiratory depression (infrequent breathing, shallow breathing, change in skin colour)
- pupillary constriction — pinpoint pupils
- slow pulse and low blood pressure.

Some of the signs of opioid overdose are more pronounced when the patient has ingested other substances with additive depressant effects, such as alcohol, benzodiazepines or barbiturates (see Chapter 10).

Opioid Withdrawal

Withdrawal from opioids (including withdrawal from methadone) may be characterized by some, or all, of the following:

- anxiety
- weakness
- restlessness, irritability
- nausea, vomiting, loss of appetite
- abdominal cramps
- diarrhea
- runny nose, watery eyes
- insomnia
- muscle tension, cramps, spasm, twitching (hence "kicking the habit")
- sweating, coldness, shivering, gooseflesh (hence "cold turkey")
- yawning
- "bone" aches in limbs and lower back.

While for most opioids the objective signs of withdrawal tend to subside within days or weeks, the subjective experience of withdrawal may last months. The degree of

physical dependence, as determined by the amount of opioids used, along with the frequency of use and the duration of use, determines the severity of the objective signs of withdrawal. The severity of the addiction (see Chapter 1), as well as the degree of physical dependence, determines the severity and duration of the subjective experience of withdrawal. The duration of action of the opioid also determines the duration of withdrawal. If an opioid is discontinued slowly, the objective signs of withdrawal are less severe.

While the signs and symptoms that accompany abrupt discontinuation of methadone are similar to the signs and symptoms that accompany abrupt discontinuation of other opioids, there are some differences. Due to its long duration of action (see below), withdrawal associated with methadone starts later and lasts longer than withdrawal associated with short-acting opioids like heroin. The objective withdrawal following discontinuation of methadone is therefore less severe than the withdrawal following discontinuation of short-acting opioids such as heroin. Nevertheless, the subjective experiences (symptoms) that follow discontinuation of methadone may be equally or even more distressing than those that follow discontinuation of short-acting opioids. This may be a consequence of the longer duration of methadone withdrawal or of the context in which it takes place (e.g., involuntary discontinuation of MMT).

Abrupt discontinuation of high-dose opioids (including methadone) in physically dependent individuals is not as dangerous as abrupt discontinuation of high-dose alcohol, benzodiazepines or barbiturates in physically dependent individuals. The latter can be life-threatening and can present with delirium or convulsions. Nevertheless, opioid withdrawal can have serious consequences for pregnant opioid users and for opioid users with serious medical conditions such as AIDS (spontaneous abortion or premature labour, and worsening of the condition, respectively; see Chapter 10).

Methadone Pharmacokinetics

Absorption

- When given orally, methadone is effectively absorbed from the gastrointestinal tract within approximately 30 minutes.
- Oral bioavailability is approximately 90 per cent.
- Peak plasma levels occur about two to four hours after oral ingestion.

Distribution

- Methadone is extensively bound to plasma proteins.
- Volume of distribution is 3.8 ± 0.6 L/kg (Intrurrisi et al., 1987).
- Elimination half-life (t1/2) is 35 ± 12 hours (Intrurrisi et al., 1987). The long half-life permits for once-daily dosing. It also results in taking longer for plasma levels to reach steady state than with most other opioids. It takes about five to seven half-lives before plasma levels reach steady state.
- The duration of action of methadone in suppressing opioid withdrawal is dose dependent, and with adequate therapeutic doses, withdrawal is typically suppressed for 24 to 36 hours.
- There is wide variability in plasma methadone levels among individuals prescribed the same dose. There is no consensus regarding interpretation of blood levels in clinical practice.
- In pregnancy, methadone passes through the placenta to the fetus.
- Methadone is excreted into breast milk in small amounts.

Metabolism

- Methadone is metabolized in the liver by demethylation and glucuronidation.
- It is predominantly metabolized by the cytochrome P450 system, mainly by CYP3A4.
- Active metabolites methadol and normethadol are produced in small amounts. The primary metabolite of methadone, EDDP (2-ethylidene-1,5-dimethyl-3, 3-diphenylpyrolidine), has no significant pharmacological activity.
- Metabolism by CYP3A4 is subject to the induction and inhibition effects of many other drugs (see Chapter 11).

Excretion

- Methadone is excreted in the urine and feces both as unchanged methadone and in the form of metabolites.
- Urinary excretion of methadone and metabolites is dose dependent. Excretion of the unchanged parent compound becomes the major route of excretion when the dose exceeds 55 mg daily. On lower doses, the majority is excreted as EDDP.
- Renal re-absorption of the parent compound decreases as urine pH decreases.

Some clinical implications of methadone's pharmacokinetic properties are as follows:

- If vomiting occurs 30 minutes or more after ingestion, replacement dosing is not necessary.
- There is no "rush" associated with methadone ingestion, and in patients on a stable dose, its psychoactive effects are minimal.
- Early in treatment, the methadone administered is largely accumulating in protein

binding, body fat and other sites of storage that contribute to the long elimination half-life, hence the duration of perceived action will initially increase with each dose.

- The large inter-individual variability in elimination half-life and level of tolerance make the clinical response to a given dose difficult to predict, hence the need to start with low doses and slowly adjust upwards.
- The long elimination half-life contributes to less severe physical withdrawal symptoms on dose decreases or discontinuation compared with symptoms from most other opioids.
- The long duration of action allows once-daily dosing for the treatment of opioid dependence.
- The clinical utility of routinely monitoring methadone plasma levels has not been established.
- Infants born to mothers on methadone maintenance may show signs of opioid withdrawal.
- Mothers in MMT should give careful consideration to breastfeeding in view of the fact that a small amount of methadone is excreted in breast milk.
- The presence of EDDP, the principal metabolite of methadone, in urine can be used as an indicator of compliance.

The Differences between Heroin and Methadone

Some of these differences have already been discussed above. The U.S. Department of Health and Human Services sums up the differences as follows:

In contrast to heroin, methadone

- is better absorbed orally; it is slower-acting than injected heroin (30 minutes for effect vs. immediate effect)
- does not cause drowsiness or "euphoria" (in stabilized patients)
- does not cause impairment in thinking, behaviour or functioning
- does not dull normal emotions and physical sensations
- diminishes opioid craving
- reduces the likelihood of heroin-induced "euphoria"
- will continue to be effective with long-term use without dosage increases;
- is medically safe
- is longer-acting than heroin (24–36 hours vs. 3–6 hours) and is administered less frequently (once/day vs. 3 or more times/day)
- decreases drug-seeking behaviour.

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chapter

4

Prescriptions in Community Pharmacies

Eva Janecek, BSc Phm
Anne Kalvik, BSc Phm
and Pearl Isaac, BSc Phm

PRESCRIPTIONS IN COMMUNITY PHARMACIES

Legislative Framework and Authorization

Methadone is a "straight" narcotic. All federal and provincial statutes and regulations that apply to straight narcotics also apply to methadone. For example:

- Refills, telephone or electronic prescriptions are not permitted.
- Electronic prescriptions may be used for preparation of doses; however no dispensing can occur until the patient presents the pharmacist with an original written prescription.

In addition, under federal law, Canadian physicians require a special authorization, issued by the federal Office of Controlled Substances (OCS), to prescribe methadone. Authorization to prescribe methadone is granted to individual physicians. For institutions (e.g., hospitals), staff physicians must be individually authorized, because authorization does not apply to the overall institution. Ontario physicians interested in becoming authorized to prescribe methadone should be advised to contact the College of Physicians and Surgeons of Ontario (CPSO) for information. The CPSO requires physicians to have formal training before they are authorized by the OCS.

Pharmacists are not required to have a special authorization to dispense methadone. Nevertheless, the Ontario College of Pharmacists (OCP) recommends that pharmacists involved in methadone dispensing attend training offered by the Centre for Addiction and Mental Health (CAMH).

Prescription Requirements

As for any prescription, when pharmacists receive a methadone prescription, they should confirm its authenticity. Pharmacists must be satisfied that the prescriber is authorized to prescribe methadone. Pharmacists can confirm this by checking with the physician or by contacting the CPSO, OCS or OCP.

In addition to usual prescription requirements (patient's name and address, name of medication, dose, directions and amount to be dispensed, etc.), prescriptions for methadone should clearly indicate the following:

- start and stop dates for doses — there should be no confusion regarding these dates (e.g., use of the word "inclusive" after the dates is useful)
- days of the week on which doses must be ingested under the supervision of a pharmacist — unless otherwise specified, pharmacists should assume that all doses are to be ingested under the supervision of a pharmacist
- days of the week on which doses may be taken at home (take-home doses).

It is also useful for physicians to indicate the following on the methadone prescription:

- dose spelled out in words, as well as in numbers, e.g., methadone 90 (ninety) mg
- instructions "dispense in drink or juice"
- name of the dispensing pharmacy (patient's choice is respected)
- instructions to the pharmacist to supervise ingestion
- reference to dispensing daily
- days when dispensing is contingent on providing a urine sample to the lab (if applicable).

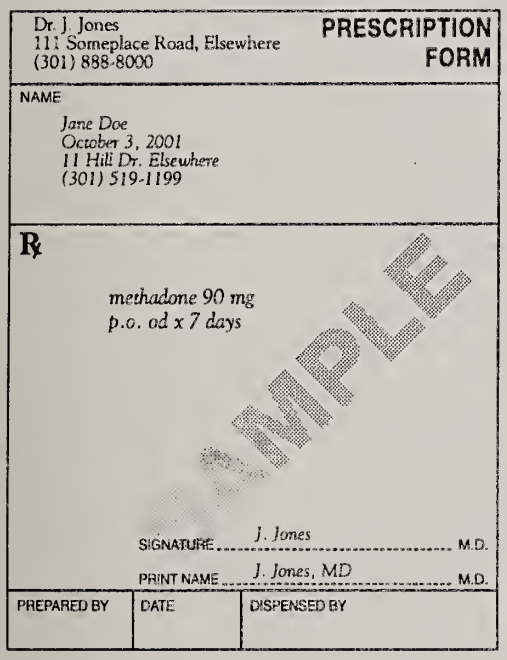
Hash marks (lines) through any blank spaces on the prescription help prevent the prescription from being altered. A physician may direct the pharmacist to omit the mg dose on labels for take-home doses when the patient has requested a "blind" taper (see "Methadone Discontinuation" in Chapter 6).

For their prescription pads, some physicians use coloured paper that changes in appearance when photocopied, or they use currency-like/coloured "watermark" printing. Others have numbered prescription pads or keep copies for their files. An example of a prescription form designed specially for methadone can be found in Appendix 5.

When writing a new prescription for a new (i.e., higher or lower) dose when a prescription for the old dose is still valid, the prescriber should indicate prominently "cancel previous prescription" and "dose change." This helps prevent both prescriptions from being filled at different pharmacies.

Sample Prescriptions

Incomplete Prescription



Problems with this prescription:

- no start and stop dates (date prescription was written may not necessarily be start date)
- no directions provided with respect to doses to be supervised by the pharmacist
- no directions for carry doses
- not clear that dispensing must occur daily
- possible to interpret that all doses should be dispensed at once in one container, or undiluted as stock solution
- easy to alter the numerical dose (e.g., to 190 mg) or the number of days.

Complete Prescription (without Take-home Medication)

Dr. J. Jones
111 Someplace Road, Elsewhere
(301) 888-8000

PRESCRIPTION FORM

NAME

Jane Doe
October 3, 2001
11 Hill Dr. Elsewhere
(301) 519-1199

℞

Methadone 50 (fifty)
mg daily in orange drink
m:drink daily under
observation
no carries
To start: Oct. 3, 2001
To end: Oct. 10, 2001
(Inclusive)

SAMPLE

SIGNATURE *J. Jones* ---------- M.D.

PRINT NAME *J. Jones, MD* ---------- M.D.

PREPARED BY	DATE	DISPENSED BY

Complete Prescription (with Take-home Medication)

Dr. J. Jones
111 Someplace Road, Elsewhere
(301) 888-8000

PRESCRIPTION FORM

NAME

Jane Doe
October 3, 2001
11 Hill Dr. Elsewhere
(301) 519-1199

℞

Methadone 50 (fifty)
mg daily
m:drink Mon. to Fri.
inclusive (observed)
carry Sat. & Sun.
To start: Oct. 3, 2001
To end: Oct. 10, 2001
(Inclusive)

SAMPLE

SIGNATURE *J. Jones* ---------- M.D.

PRINT NAME *J. Jones, MD* ---------- M.D.

PREPARED BY	DATE	DISPENSED BY

Prescriptions not in Accordance with the Guidelines

If the pharmacist receives a prescription that is written contrary to the Guidelines, he or she should discuss this with the prescriber. The dialogue with the physician should be documented.

If, according to the pharmacist's professional judgement, it is unsafe to fill the prescription, and the physician cannot be persuaded to change it, the pharmacist may be justified in refusing to fill it. In such cases, the pharmacist should inform the physician and the patient of the decision and document the reasons. The pharmacist should also consider reporting the incident to the CPSO and OCP.

chapter

Preparation and Storage

5

Anne Kalvik, BSc Phm
Eva Janecek, BSc Phm
and Pearl Isaac, BSc Phm

PREPARATION AND STORAGE

Summary

The pharmacist purchases methadone as a powder.

First, a stock solution of methadone in distilled water is prepared in a convenient concentration, such as 5 mg/mL. Then, prior to dispensing methadone to the patient, the pharmacist measures a volume of stock solution equivalent to the dose and further dilutes it to approximately 100 mL with a vehicle such as orange juice or drink.

Good pharmacy standards of practice should be used for preparation of methadone doses as for other extemporaneous compounds. These include accurate calculations and appropriate compounding techniques.

Record keeping should be maintained as for other "straight" narcotics.

Availability

In Canada, methadone is available to pharmacists in powder form from drug wholesalers or from pharmaceutical chemical suppliers. Methadone powder can be obtained in small quantities (e.g., 1 g size) if necessary. Pharmacists must then prepare an extemporaneous stock solution.

Preparation of Stock Solution

Prepare a stock solution of methadone in distilled water in a concentration that is both convenient and easy to measure for the pharmacy's patient population (e.g., for a 5 mg/mL stock solution, dissolve 1 g (1000 mg) of methadone HCl powder in 200 mL distilled water).

For situations in which the dose is being adjusted by 1 mg increments or decrements, it may be useful to make more dilute solutions, such as 1 mg/mL, to permit more accurate measurement of such small doses.

Stability of Stock Solution

Stock solutions of methadone should be stored in light-resistant glass containers.

Methadone in water is very stable. If preservatives are not used, shelf-life is considerably shortened due to the possibility of bacterial growth. Regular checks for signs of bacterial growth should be made if preservatives are not used. If possible, it is preferable to keep stock solutions of methadone under refrigeration. The shelf-life of methadone stock solutions with preservatives is at least two years from the date of preparation. An example of preservatives that can be added to prevent bacterial growth: methylparaben 0.5 g/L and propylparaben 0.2 g/L.

Preparing quantities of stock solution without preservatives, sufficient to last one to two weeks, may be practical for most community pharmacies.

Preparation of Final Dosage Form

Prior to dispensing to the patient, the pharmacist should always further dilute stock solutions of methadone to approximately 100 mL with a vehicle such as orange drink or juice.

Accurate measuring devices should be used to draw up doses of stock solution for dilution with orange juice, e.g., syringe, measuring pump, etc. Note that syringes may have an error rate of up to 10 per cent. Having the same person measuring the doses can minimize error. Physicians and pharmacists should be aware of these issues especially when small dose changes are made (e.g., 1 mg).

Methadone stock solution is further diluted because:

- a vehicle such as orange juice helps mask the bitter taste of methadone
- methadone in water can be injected — the addition of orange juice deters injection due to its excipient and sugar content
- large volumes are more difficult to inject or modify for injection
- large volumes are difficult to retain in the mouth, thus helping to reduce diversion.

Examples of vehicles that have been used to further dilute methadone stock solution include orange-flavoured Tang® or other brands of crystals, orange juice, apple juice,

grape or cherry-flavoured Crystal Lite® or other brands of artificially sweetened crystals. Products with artificial sweeteners may be used for diabetic patients.

Pharmacy staff in the dispensary, or other patients or their children, should never, under any circumstances, consume the juice used to dilute methadone doses as a beverage. Similarly, cups used for dispensing observed doses should not be used by the staff for any other purpose. Bottles containing stock solution and vehicle should both be clearly labelled. Methadone stock solution should be stored in a unique light-resistant bottle that will prevent confusion with other clear, colourless liquids. If more than one concentration of stock solution is being used, each should be clearly differentiated and identified. *Good compounding practices must be followed at all times.*

Stability of Final Dosage Form (Methadone in Juice)

Methadone stability is not altered when mixed with juice containing sugar or an artificial sweetener.

The shelf-life of methadone in juice or drink depends on the shelf-life of the juice used for dilution. Factors that influence shelf-life of the vehicle include:

- what type of juice or drink was used as fresh juices have a much shorter shelf-life than drinks prepared from powders
- how long it has been open (if bottled or canned juice is used)
- how it was prepared
- how it has been stored.

Take-home doses should be refrigerated in order to keep the vehicle fresh. If take-home doses cannot be stored in a refrigerator (e.g., while the patient is on holiday in a car or aeroplane), the pharmacist should recommend use of a secure cooler with ice packs. Patients travelling by air should carry their medication in their carry-on personal luggage.

chapter

6

Methadone Dosing Issues

Pearl Isaac, BSc Phm
Anne Kalvik, BSc Phm
and Eva Janecek, BSc Phm

METHADONE DOSING ISSUES

Initial Dose

The purpose of the initial dose is to reduce opioid withdrawal symptoms. The initial dose should not exceed 15 to 30 mg per day. The initial dose depends on the patient's history, signs and symptoms. The low initial dose minimizes the risk of overmedication. Lack of tolerance to the effects of higher initial methadone doses has resulted in fatal methadone overdose. Fatal overdose has resulted from a dose as low as 40 mg daily for three days (see Safety of Methadone, Chapter 3).

Initial Stabilization

The goal is to achieve an optimal maintenance dose as quickly as possible. At the same time however, it is important to balance the goal of quickly stabilizing the patient against the risk of overdose.

Based on pharmacokinetic principles, steady state levels for methadone are achieved in five to 10 days (about five half-lives). Nevertheless, with careful clinical monitoring, doses in the first week of treatment can be increased every three to four days, as long as the prescriber remains mindful of the accumulation of methadone in body tissues.

The patient should be assessed frequently to review the safety and effectiveness of the methadone dose until he or she is stable. Each dose adjustment should be in the range of 5 to 15 mg — depending on the emergence and severity of opioid withdrawal, opioid craving and limiting adverse effects, such as sedation — until symptom relief or a dose of 60 mg is reached.

If a daily dose of 60 mg is reached, the rate and amount of dose adjustment should be no more than 5 to 10 mg every seven to 14 days.

Maintenance Dose

Most patients are stabilized within two to eight weeks of initiating methadone maintenance treatment (MMT).

The appropriate maintenance dose of methadone is the dose that works best for the individual patient. An appropriate dose should eliminate withdrawal symptoms and minimize or eliminate opioid craving; the effects should last until the next day while avoiding sedation and other limiting side-effects. For most patients this dose is between 50 and 120 mg. Some patients will do well on doses as low as 20 to 30 mg, while others may require doses above 120 mg.

Research evidence suggests that higher daily methadone doses (i.e., more than 60 mg) are more effective than lower doses (i.e., less than 60 mg) for retaining patients in treatment and decreasing illicit opioid use.

Timing of Doses

Ideally, daily methadone doses should be taken 24 hours apart.

In pharmacies with extended hours (e.g., 24-hour stores) patients have been reported to ask for an early morning (e.g., 1 a.m.) dose after having received a late-evening dose a few hours earlier. In such circumstances the pharmacist should not medicate at that time and should advise the patient that it would be unsafe to be medicated after such a short interval. The patient should be asked to return at least 12 hours after the previous dose. Explaining that this is a safety issue helps minimize conflict with the patient. A communication log should help to prevent inadvertently medicating a patient only a few hours after the previous dose (See Chapter 7).

Divided Doses

Some pregnant patients may benefit from divided dosing during the initial stabilization period. This may be most easily done in a hospital setting. Once the daily dose requirement is determined, the total dose is consolidated into a single daily administration. Some patients also may require twice-daily dosing during the last trimester (see below, Dosing in Pregnancy).

A very small number of individuals are fast metabolizers of methadone. These patients can be identified by doing serial plasma methadone levels. Such patients may benefit from twice-daily dosing rather than a larger single daily dose.

Missed Doses

Methadone is most effective when patients comply with therapy. Missed dose pickups should be reported to the prescriber in a timely fashion. Reporting all missed dose pickups will help the prescriber assess the patient's progress and stability. Some pharmacists use a fax form for this purpose. Missed dose pickups may indicate a variety of problems, including relapse to alcohol or other drug use.

Patients who have not picked up their methadone for one or two days can be given their prescribed dose provided that they are not intoxicated (see "Intoxicated Patients," Chapter 7). If the patient is intoxicated, methadone should be deferred until a physician examines the patient, or the pharmacist assesses that it is safe to medicate.

Patients who have not picked up their dose for three days consecutive or more should not be medicated, even if there is a valid prescription, until they have been reassessed by their prescriber. The prescription should be put on hold. If the dose was 30 mg or less, the prescriber may ask that the prescription be continued after the patient has been assessed.

Patients who have interrupted their therapy may have lost tolerance to the effects of methadone and it may be unsafe to medicate at their previous dose. They may be restarted at 30 mg per day (or less), or up to half their previous dose. Factors that may influence the dose include: clinical presentation, previous maintenance dose, number of doses missed and use of other opioids. Daily increases of no more than 15 to 20 mg should be administered until the previous maintenance dose is achieved or the patient is stabilized on a lower dose.

Patients who are not able to contact the prescriber and are in withdrawal due to missed doses (perhaps because they did not keep their appointment) should be counselled to use symptomatic treatment for opioid withdrawal. They can be reassured that because methadone is long-acting, missing one dose should not result in significant withdrawal. Withdrawal does not usually begin immediately, and it is often less severe than withdrawal from illicit opioids. Pharmacists can recommend acetaminophen or ibuprofen for muscle aches and pains, dimenhydrinate for nausea and vomiting, and loperamide for diarrhea.

Vomited Doses

Vomited methadone doses are not replaced, in full or in part, unless the pharmacy or clinic staff directly observe emesis. For pregnant patients, the physician may decide to prescribe a replacement dose even if the pharmacy or clinic staff did not observe emesis. It is very important that pregnant patients not go into withdrawal. Pharmacists should inform the prescriber and obtain a new prescription for the replacement dose.

Methadone is rapidly absorbed from the gastrointestinal tract. Absorption of a methadone dose is considered complete within 30 minutes after dosing. A common approach is to replace the full dose if emesis occurred within 15 minutes of dosing, and to replace half the dose if the patient vomited 16 to 30 minutes after dosing. For patients who are receiving a dose over 150 mg, replacement doses may be lower than suggested above. The dose is not replaced if vomiting occurred more than 30 minutes after dosing. It should be kept in mind that even with severe vomiting, only about 40 per cent of the stomach contents can be emptied. For patients who vomit repeatedly (on the same day or consecutive days), replacement doses should be lower than outlined above to prevent intoxication and possible overdose. A physician must order all replacement doses. If a patient complains of feeling nauseated prior to being medicated, consider delaying medication or pre-medicating with an antinauseant. Also suggest that methadone be sipped slowly and that the patient remain in the pharmacy for 15 to 30 minutes after being medicated.

Dosing in Pregnancy

Pregnancy in a heroin-dependent woman is an urgent indication for MMT. Treatment leads to better outcomes for the mother and baby than continued heroin use in this high-risk situation (see Chapter 12). The goal of methadone dosing in pregnancy is to maintain the patient on the minimum dose required to keep the patient comfortable while maintaining abstinence from illicit opioids.

Ideally, initial treatment in hospital is preferred, where the patient can be more easily and quickly stabilized and monitored for withdrawal and fetal distress. At the same time, other prenatal issues can be addressed. Generally, the patient is assessed for withdrawal every four to six hours. Withdrawal symptoms are treated with 5 to 10 mg of methadone. When stabilized, the previous day's methadone dose is consolidated into one dose the next morning. If needed, supplemental small doses may be given when appropriate for withdrawal symptoms. Careful clinical monitoring is essential. Most patients are discharged on 35 to 60 mg per day. Some clinicians recommend

keeping the daily dose below 80 mg, if possible. Methadone dosing should be adequate to prevent withdrawal and to minimize craving for the use of other opioids. If hospitalization is not feasible, the patient can be stabilized on an outpatient basis.

Studies in pregnant methadone patients show plasma levels somewhat lower after a given dose during pregnancy (especially in the third trimester) than after delivery. This is owing to the increased fluid space, a large tissue reservoir for storing methadone, and drug metabolism by both the placenta and the fetus.

Some methadone-maintained pregnant women might develop signs and symptoms of withdrawal in the third trimester due to the increases in blood volume and metabolic changes specific to pregnancy. These patients may need an increase in their methadone dose or twice-daily dosing ("split dosing") in order to maintain the same plasma methadone level. After delivery, the dose requirements are reviewed and doses are frequently reduced.

During pregnancy, if the option of withdrawal from methadone or dose decrease is elected, it should be attempted in the second trimester and not be started during the first 14 weeks of gestation or after the 32nd week because of risks to the fetus. The dose should not be decreased by more than 5 mg every one to two weeks to prevent fetal distress and the onset of preterm labour. (See Chapter 12).

Methadone Discontinuation

Patient-Initiated or Voluntary

Taper

- While the effectiveness of long-term methadone maintenance is well recognized, there may be times when the patient wants to start tapering and eventually discontinue the use of methadone (see above for methadone dose reduction during pregnancy).
- At such times, the patient should be made aware of the risk of relapse to drug use. It may also be helpful to incorporate relapse prevention techniques into the counselling component.
- The rate of taper can vary widely among methadone patients and may be patient directed. While a maximum taper rate of 5 mg per week is recommended, the rate of methadone taper can be increased or decreased according to each individual patient's response and desire. At times, the patient may ask to be held at a dose for some time before continuing to taper. Slower tapers have been shown to be more successful than rapid tapers.

- The rate of taper is reduced as the dose is decreased below 20 mg. Many clients find the last part of the taper particularly difficult.

Abrupt Self Discontinuation

- Patients on MMT should be strongly discouraged from abruptly discontinuing treatment because of the high risk of relapse to heroin/opioid use.
- Patients on daily doses of methadone are physically dependent on this drug. Those on high doses are particularly at risk of experiencing severe withdrawal symptoms if the medication is abruptly discontinued.
- With abrupt discontinuation, symptoms of withdrawal emerge gradually and are not usually observed until 36 to 48 hours after the last dose. These symptoms include loss of appetite, abdominal discomfort, nausea and vomiting, feelings of hot and cold, sweating, muscle and bone pain, headache and insomnia. Increases in blood pressure, body temperature, pulse, respiratory rate and pupillary size may also occur. Withdrawal symptoms peak at about 72 hours after the last methadone dose and may continue at this level for about two weeks. The withdrawal syndrome then declines very gradually, typically ending at the sixth or seventh week. In some patients, symptoms such as insomnia, depression, anxiety or craving may be protracted, lasting for weeks or months.

Involuntary

- Patients who are being discharged involuntarily are usually maintained at their regular dose until they are transferred to another physician or program.
- If the decision is made to discontinue methadone, the dose should be tapered at a rate of no more than 5 mg every three or four days. During the last two weeks of the taper, additional medications may be offered to decrease withdrawal symptoms (e.g., clonidine, loperamide, NSAIDs, dimenhydrinate).

chapter

7

Dispensing and Observed Self-administration

Eva Janecek, BSc Phm
Pearl Isaac, BSc Phm
and Anne Kalvik, BSc Phm

DISPENSING AND OBSERVED SELF-ADMINISTRATION

The pharmacist dispensing methadone should be familiar with the use of the medication in treating opioid dependence, as well as with its pharmacology, pharmacokinetics, adverse drug reactions and drug interactions.

Pharmacists are not required to have formal training before filling prescriptions for methadone. Nevertheless, the Ontario College of Pharmacists (OCP) recommends that pharmacists attend the physician-pharmacist methadone maintenance treatment (MMT) training program offered by the Centre for Addiction and Mental Health (CAMH). The OCP also recommends that pharmacists update their knowledge by attending continuing education events and studying the literature. Networking with other pharmacists practising in the area of MMT is also strongly recommended.

Applicable guidelines (e.g., *Methadone Maintenance Guidelines* published by the College of Physicians and Surgeons of Ontario, the Centre for Addiction and Mental Health, and the Ontario College of Pharmacists, and included with this Guide) need to be available to pharmacy staff.

An understanding of addiction in general and opioid addiction in particular will enable the pharmacist to understand this patient population and its specific issues and to make referrals when appropriate (see Chapter 1).

All staff working in the pharmacy who interact with MMT patients should understand the principles of preserving the confidentiality of information about individual patients.

Communication

Communication among the pharmacist, physician and all other health care providers involved in MMT is essential for treatment success. Pharmacy staff should maintain the same level of respect for patient confidentiality and professionalism expected in all aspects of their work.

Communicating with Prescribers and Pharmacists

For patients new to the pharmacy, it is helpful to ask the patient if he or she has been in MMT recently to find out whether the patient is new to MMT or is changing pharmacies.

Patients New to Methadone Maintenance Treatment

Ideally the prescriber should contact the pharmacy chosen by the patient when the prescriber is starting a new patient in MMT. If this does not occur, the pharmacist should take the initiative to establish contact. *The pharmacist is obligated to be certain that the physician is authorized and that the prescription is authentic.* Where the methadone prescriber is unknown to the pharmacy, this contact should be an opportunity for the pharmacist and the physician to:

- confirm the physician's authorization (see Chapter 4)
- discuss mutual expectations, such as physician and pharmacist availability for discussion of concerns about patients.

The discussion between the prescriber and pharmacist should also cover:

- relevant clinical issues, such as a current alcohol/drug problem, that the pharmacist should be aware of (may require that the pharmacist pay greater attention to monitoring for intoxication), or other conditions such as cognitive impairment or speech impediment, which may be mistaken for intoxication
- any other relevant patient issues (e.g., dispensing of methadone in a sugar-free diluent due to diabetes).

A physician's call prior to receiving the first methadone prescription prepares the pharmacist for the patient's arrival, and allows the pharmacist to fill the first methadone prescription efficiently and to focus on patient dialogue. Administrative tasks, such as verifying that the physician is authorized, are ideally done prior to the patient's arrival. The patient is commonly anxious prior to the first dose. In fact, the patient may have spent a considerable amount of time with the prescriber and/or counsellor before arriving at the pharmacy. Focusing on pharmacist-patient dialogue can facilitate a smooth start.

Patients Changing Pharmacies

Patients are free to obtain their methadone from a pharmacy of their choice. However, the prescriber should know at all times where each patient is filling his or her methadone prescription. This is essential for maintaining physician-pharmacist communication.

The pharmacist needs to gather the same information as for a new patient and to confirm with the physician and/or previous pharmacy:

- whether any outstanding methadone prescription is being filled at the previous pharmacy
- when the patient was last medicated
- how many take-home doses (if any) were dispensed.

If the pharmacist does not verify these facts, the pharmacist may be putting the patient at risk of double-dosing.

Checklist of Physician-Pharmacist Communication

At the beginning of treatment:

- authorization (p. 45)
- contact with the prescriber after hours
- background information on patient
- pharmacy hours of operation, including weekend and holiday closures.

At the beginning of treatment and on an ongoing basis:

- missed doses (p. 57) (Do not fill prescription after three missed doses before consulting with prescribing physician.)
- vomited doses (p. 58)
- lost or stolen take-home doses (p. 72)
- over- or undermedication with methadone
- intoxication (p. 67)
- observed behaviour
- suspected diversion (p. 75)
- guest dosing arrangements (p. 69)
- other prescribed medications (e.g., opioids from dentists or emergency departments).

Communicating with the Patient

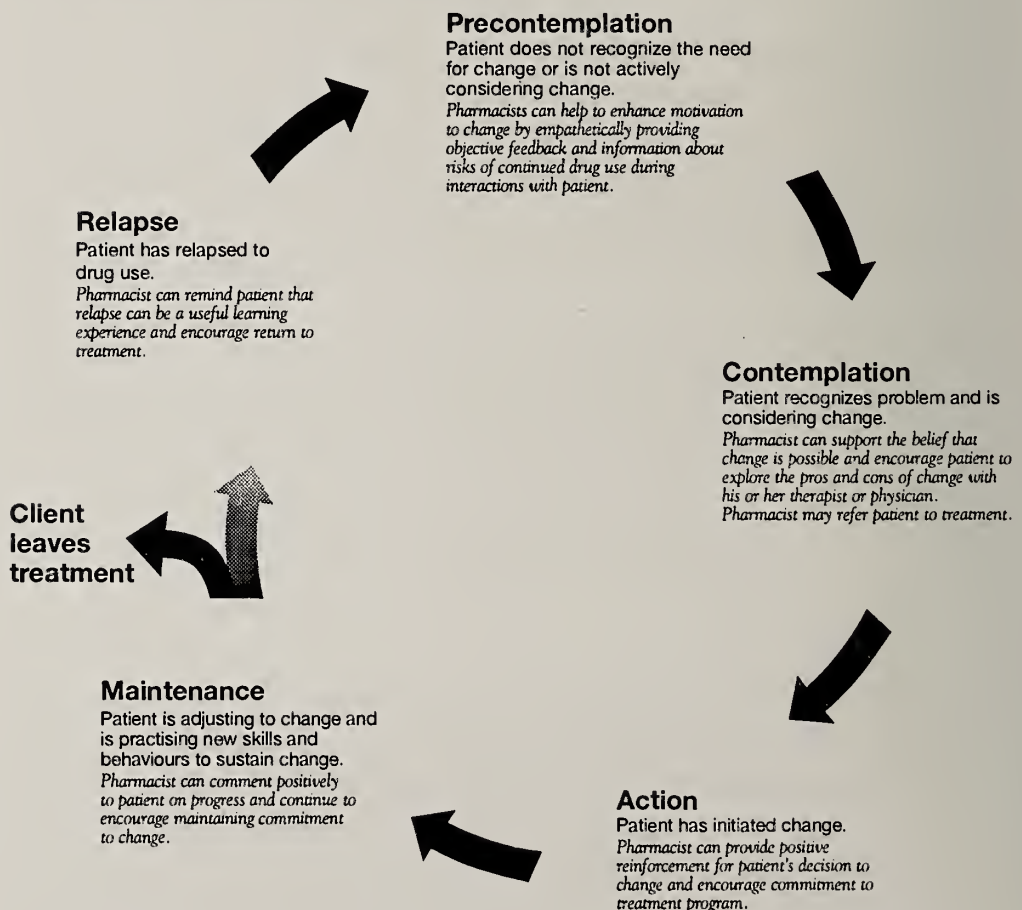
Stages of Change

Opioid dependence is a chronic and relapsing disorder. Pharmacists have many opportunities during their interactions with patients to encourage positive change. One well-known theory of how individuals with substance use problems move from

substance use to recovery is the Stages of Change model. The model describes five basic stages that substance users move through on their way to recovery: precontemplation, contemplation, action, maintenance and relapse. It attempts to explain why some people respond quickly to problems while others resist.

Patients experience change differently. Some move quickly through the stages, while others move more slowly and may remain "stuck" in one stage. Other patients may skip or repeat stages. One of the strengths of the model is its acknowledgment that change is rarely linear — that relapse occurs. Relapse, rather than seen as a totally negative experience, is looked upon as an opportunity to learn from previous attempts to change and as part of the movement towards long-lasting change. The pharmacist on the front line of treatment who can identify where the patient is on the continuum of change can better anticipate the patient's response and is able to encourage change (see diagram).

Overview of Stages of Change*


Precontemplation
Patient does not recognize the need for change or is not actively considering change.
Pharmacists can help to enhance motivation to change by empathetically providing objective feedback and information about risks of continued drug use during interactions with patient.
Contemplation
Patient recognizes problem and is considering change.
Pharmacist can support the belief that change is possible and encourage patient to explore the pros and cons of change with his or her therapist or physician.
Pharmacist may refer patient to treatment.
Action
Patient has initiated change.
Pharmacist can provide positive reinforcement for patient's decision to change and encourage commitment to treatment program.
Maintenance
Patient is adjusting to change and is practising new skills and behaviours to sustain change.
Pharmacist can comment positively to patient on progress and continue to encourage maintaining commitment to change.
Client leaves treatment
Relapse
Patient has relapsed to drug use.
Pharmacist can remind patient that relapse can be a useful learning experience and encourage return to treatment.

*Adapted from Prochaska, J.O., and DiClemente, C.C. (1982). Transtheoretical therapy: Toward a more integrative model of change. Psychotherapy: Theory, Research and Practice, 19(3), 276–288.

Initial Dialogue

As with any other prescription, pharmacists should provide information and counselling to patients filling prescriptions for methadone. This is particularly important for patients new to MMT. Written information on methadone (e.g., patient information brochures available from the Centre) can also be provided (see Appendix 1).

Methadone maintenance patients should be treated with the same respect and courtesy as any other customer of the pharmacy. By creating a supportive environment the pharmacist can maximize the opportunity to build trust and thus be better able to contribute to the patient's progress in treatment.

The pharmacist should:

- ask the patient about his or her knowledge of methadone and MMT — this helps either to reinforce the patient's knowledge or to correct misunderstandings
- encourage abstinence from illicit opioids to hasten achieving the optimal methadone dose, keeping in mind that methadone steady state is reached in about five to 10 days (initially and after each dose change)
- explain that methadone is generally well tolerated and review the most common adverse effects: sweating, constipation, drowsiness, sexual problems, weight gain
- warn of possible additive adverse effects when methadone is combined with other CNS depressants such as alcohol, and encourage the patient to discuss any possible adverse effects with the prescribing physician, as well as with the pharmacist
- review the patient's current medication profile and encourage the patient to disclose to the pharmacist all future prescription, over-the-counter and herbal medications to maintain a complete patient profile
- orient the patient to pharmacy procedures, such as dispensing hours, required identification, observation of ingestion, discussion with staff after the dose is ingested to ensure that the dose is swallowed, and disposal of the medication cup
- remind the patient of the need to inform a dentist or another physician that he or she is receiving methadone if another opioid is being prescribed. Explain to the patient that this is done for safety and legal reasons. For example, analgesics such as nalbuphine may precipitate withdrawal in a methadone-maintained patient. Not informing a dentist/physician when receiving a second opioid is also a legal offence ("double doctoring")
- advise the patient to refrain from eating foods with poppy seeds because they may cause opioid-positive urine samples
- inform the patient that in order to maintain confidentiality, pharmacy staff will not pass messages between patients and their friends or relatives

- discuss mutual expectations with respect to behaviour and payment for medications
- discuss the verbal or written agreement (see Appendix 2).

Ongoing Dialogue

Periodically ask patients how well the medication is working, whether they are taking any medications that you might not have in their patient profile, and whether they have any questions. Use positive changes in patients' appearance or behaviour as an opportunity to provide positive feedback and encourage patients.

Methadone Dispensing Area

Pharmacies that help care for numerous MMT patients may set aside an area, set apart from the rest of the dispensary, for dispensing and observing the ingestion of methadone. Providing these patients with additional privacy (i.e., not having their ingestion of methadone witnessed by other, possibly disapproving, customers) may help to protect them from further stigmatization.

Patient Identification

- Positive identification of the patient is essential; some pharmacies have a photo on file; others ask for picture identification.
- Using the patient's name when handing out the medication further ensures that the correct person is being medicated.
- Some programs and community physicians have a procedure that involves the patient in bringing proof (usually a slip of paper initialled by the laboratory staff) that he or she left a urine sample as requested by the physician. The program or community physician determines the consequences of not bringing a lab slip on the days specified on the prescription, and communicates these consequences to the pharmacist.

Supervised Ingestion

- Prior to administration to the patient, the stock solution of methadone must always be further diluted to approximately 100 mL with a vehicle such as orange drink.
- Methadone should never be given to the patient in a water solution that can easily be injected.
- Prior to dispensing, the pharmacist must ensure that it is safe for the patient to ingest methadone, i.e., that the patient does not appear intoxicated (see below).
- The pharmacist should observe the patient for changes in appearance and behaviour, and note positive changes to the patient and physician. Negative changes such as

neglect of hygiene, grooming, or increased anxiety or agitation, may indicate a variety of problems and should be communicated to the prescriber.

- A patient ingesting methadone in the pharmacy should be directly observed by the pharmacist to ensure that the entire dose is swallowed. This ensures compliance and minimizes diversion. Having the patient speak to the pharmacist after the dose is taken helps to confirm ingestion.
- The pharmacist should observe that the entire dose is emptied from the cup to ensure compliance. The physician should be informed if the patient discards part of the dose.
- For a patient with carry privileges, periodic observation of ingestion by the pharmacist ensures consumption of the entire methadone dose on those occasions. This serves as one of several methods to ensure compliance.
- Some pharmacies provide a container of water for the patient to rinse the dispensing cup after ingesting the dose.
- The dispensing cup should be discarded inside the dispensary. A garbage container should be located in such a position that the patient can easily dispose of the cup but cannot remove any of its contents.
- The garbage container holding dispensing cups should be discarded safely to prevent other customers or children from handling the discarded dispensing cups.
- If any patient, particularly one receiving take-home doses, either arrives in apparent withdrawal or exhibits intoxication after being medicated, the prescribing physician should be notified.

Intoxicated Patients

- All patients must be assessed for intoxication prior to medicating with methadone.
- Assess for symptoms such as slurred speech, ataxia, drowsiness or unusual behaviour. To test alcohol levels, some pharmacies have breathalysers that they use with the agreement of the prescriber. If levels above a certain threshold are detected, (e.g., 30 or 50 mg%), methadone is not dispensed until the alcohol level falls below that threshold.
- If the patient is intoxicated, medicating should be deferred until the patient has been seen by the prescriber or until, in the opinion of the pharmacist, the intoxication has resolved. Despite the possibility of a patient suffering opioid withdrawal, it is safer to delay medicating or to refuse to medicate an intoxicated patient; opioid withdrawal is not life-threatening, but adding methadone to the other drugs already consumed by an intoxicated patient may be.
- Try to avoid confrontation with the patient by explaining that it would be dangerous to medicate at this time. If pharmacy hours allow, invite the patient to return later, at which time it might be possible to dispense the methadone.

- Warn the patient against driving a car.
- Inform the prescriber that the patient appeared intoxicated in your pharmacy.
- Clearly document your actions.

Documentation

Documentation of methadone dispensing is guided by the same legal requirements as those for other "straight" narcotics.

In addition, keeping a log (written or electronic) of the time when methadone was given to the patient is recommended. It is particularly important to have such information available in stores that are open 24 hours. All pharmacy staff must be aware of the time of dosing. If they are not, it is possible for someone to be medicated shortly before midnight on one day and shortly after midnight the next day. This could result in intoxication or overdose. The log is also used to keep track of any missed doses.

The log also provides a place where the pharmacists can note pertinent patient issues or share relevant information regarding the patient. This may then be used to inform the prescriber and/or counsellor of any concerns.

Requests to Dispense to a Person Other Than the Client

Methadone should only be given directly to the person for whom it is prescribed to ensure safety and minimize diversion. It is important to remember that unless take-home doses are specified, ingestion of each dose should be observed.

Do not dispense methadone to a police officer, since only a health care provider can supervise methadone ingestion. Ask the officer to bring the patient to the pharmacy to be medicated. Inform the prescriber of the possibility that the patient may be incarcerated.

Home Delivery

Home delivery of methadone should be reserved for emergency situations in which a patient is incapable of coming to the pharmacy, the prescriber agrees to home delivery, and the pharmacist is willing to deliver methadone and to supervise ingestion in the patient's home.

Guest Dosing

There are occasions, such as a vacation or business travel, when a methadone patient might ask to be medicated on a temporary basis at a pharmacy other than the usual one. Guest dosing generally involves situations in which the patient cannot be provided with sufficient take-home doses for the period of absence. Such situations may arise when:

- the patient is not considered sufficiently functionally stable to be given take-home doses for the time period
- the patient may be away for a long period that prevents issuing sufficient take-home doses (e.g., juice will go rancid; it is not practical to travel with a large number of containers; concern exists about loss/theft of a large number of containers).

The prescriber or pharmacist can help the patient to identify a conveniently located pharmacy that would be willing to dispense methadone on a temporary basis. The OCP or CPSO provides the names, addresses and telephone numbers of methadone-dispensing pharmacies to physicians and pharmacists. As a professional courtesy, the name of a methadone-dispensing pharmacy should not be provided to a patient without the prior consent of that pharmacy.

The patient or pharmacist should inform the methadone prescriber of the name and address of the temporary pharmacy. If the prescription at the usual pharmacy is still valid for the time the patient will be away, the physician should cancel the remainder of the prescription and write a new prescription for the temporary pharmacy.

The pharmacists at both pharmacies must communicate clearly with one another at the beginning and end of the guest-dosing period, so that everyone understands where (and when) the patient is receiving the methadone. It is imperative that double-dosing (i.e., an overlap) or missed dosing (i.e., a gap) not occur.

Take-Home Doses (Carries)

INTRODUCTION

A patient who has been maintained on methadone for at least three months and is (among other things) functionally stable, as defined in the *Methadone Maintenance Guidelines* (the "Guidelines"), may receive methadone doses intended for self-medication. In Ontario, take-home doses are commonly called "carries." The prescriber determines the number of take-home doses, with input from both the patient's counsellor and pharmacist. The number of take-home doses that are provided increases as functional stability improves up to a maximum of six per week on a regular basis (with one observed ingestion per week). Criteria for determining how many take-home doses a patient can have are included in the Guidelines.

Patient Suitability for Take-Home Doses

Functional stability is the main determinant of the suitability of methadone-maintained patients for take-home doses. Pharmacists have frequent (initially daily) contact with patients in MMT and are therefore in a good position to make objective observations with regard to positive and negative changes in the patient — to monitor patient progress and stability. This information can be critical to the prescriber's and/or counsellor's assessment of patient functional stability.

Useful information for the prescriber or counsellor includes the following:

- How regularly does the patient attend at the pharmacy?
- Is the patient's dose appropriate? Is the patient showing signs, or reporting symptoms, of opioid withdrawal or opioid intoxication?
- What patterns of behaviour have been observed?
- Does the patient appear intoxicated when coming in for methadone doses?
- Is there any improvement or deterioration in self-care (e.g., hygiene, grooming, dress)?

Other factors that the physician and counsellor consider in assessing the patient's functional stability and/or the patient's suitability for take-home doses include the following:

- How long has the patient been in MMT? (the Guidelines recommend no take-home doses for the first three months.)
- Has the use of illicit opioids and, if applicable, other drugs of abuse (including alcohol) diminished?
- Is the patient keeping medical appointments?
- Is the patient engaged in activities such as work, school or care for family members; and is the patient in (a) stable relationship(s)?
- Does the patient appear to be involved in criminal activity (e.g., recently charged with drug dealing, stealing)?
- Does the patient have a concurrent psychiatric disorder?
- Can the take-home doses be safely stored in the patient's home? Patients residing in shelters or temporary housing, or patients with "no fixed address," should pick up daily as take-home doses cannot be kept safe in those circumstances.
- Does the patient's home environment or relationships pose a risk for diversion or accidental ingestion of carry medication?

Pharmacists can play a significant role in helping the prescriber to assess the progress of the patient. Communicating observations to the physician and/or counsellor may provide the prescriber with information not available from other sources. The prescriber will then be in a better position to decide when it is safe for a patient to have take-home

doses. The pharmacist can also be instrumental in making the prescriber aware of possible relapse to alcohol and/or other drug abuse/addiction when a patient has had take-home doses for a period of time and there is apparent deterioration in the patient's appearance or behaviour. It is important to pass on information to the physician on a continuous and regular basis.

Dispensing Take-Home Doses

Take-home doses must be diluted with juice to approximately 100 mL total volume, and each day's dose should be dispensed in individual daily unit-dose bottles labelled according to the date of ingestion. Childproof safety caps are strongly recommended. The label should include a warning about the potential harm to children and non-tolerant adults.

Sample Take-Home Dose Medication Label

Pharmacy Rx #:
Address Date:

Jane Doe
Drink all at once on Saturday Sept. 29, 2001
Methadone 50 mg in orange drink

Dr. Smith

CAUTION: METHADONE MAY BE FATAL TO CHILD/ADULT

Dialogue with Patient about Take-Home Doses

The first time take-home doses are dispensed, patient counselling should include appropriate use and storage of the medication. Many pharmacists, physicians and programs have patients sign a written agreement to ensure that precautionary measures and expectations are clearly understood (see Sample Agreement in Appendix 2).

The pharmacist should emphasize that:

- take-home doses are for the patient's consumption only
- take-home doses are best stored in a refrigerator; a locked box (e.g., lockable fishing tackle box) is highly recommended, especially in households with children
- take-home doses should be consumed on the day specified on the label
- methadone can be lethal to a child or non-tolerant adult (as little as 10 mg can be fatal in children; a single day's maintenance dose of methadone (50–70 mg) can be lethal to non-tolerant adults (see Chapter 3)
- ingestion by individuals other than the patient should be considered a medical emergency, and emergency assistance (911) should be called immediately

- security of the take-home doses is the responsibility of the patient; if take-home doses are lost or stolen, police should be notified immediately to prevent possible harm to others
- misplaced, lost or stolen take-home doses are generally not replaced, as with any other narcotic (if any doses are replaced, a new prescription is required)
- empty medication bottles should be returned to the pharmacy.

Lost or Stolen Take-Home Doses

Patients should be counselled about their responsibility for the safekeeping of their medication when they first receive take-home doses. Lost or stolen take-home doses are a potential hazard. It is possible that the person who finds the medication or who has stolen it may consume or divert it. In either case, there is a risk of accidental overdose. Lost or stolen take-home doses should be reported to the police. Warnings to the public have appeared in the media in cases of lost take-home medication.

Decisions on replacing lost or stolen take-home doses are made on a case-by-case basis. A new prescription is required for replacement doses (see also Chapter 8).

Patient-Pharmacist Agreements/Contracts

To help ensure that the rights, obligations and expectations of all those involved in MMT are understood, treatment providers have found it helpful to enter into agreements with patients. Pharmacists may find it helpful to enter into verbal or written agreements with patients around pharmacy issues such as dispensing procedures and take-home doses. Pharmacists may also collaborate with the prescriber or counsellor in the preparation of a treatment contract that includes pharmacy issues.

Agreements concerning dispensing procedures may include:

- picking up during specified dispensing hours
- presenting identification before receiving medication
- providing proof of having left a urine sample before receiving medication (if directed by the prescriber, and according to instructions)
- taking medication as directed by the pharmacist
- refraining from verbal threats, assault, destructive behaviour, shoplifting, etc.
- making dispensing contingent on patient compliance with the agreement.

Agreements about take-home medication may include:

- transporting and storing medication safely

- storing methadone in the original bottle and keeping the label intact (doses should not be transferred to any other container)
- not giving away or selling medication
- returning empty medication bottles on the day following each take-home dosing period
- making dispensing contingent on patient compliance with the agreement.

It is very important that patients understand the particulars of these agreements. A follow-up discussion with patients, conducted after the agreement has been set out, helps reinforce understanding (for sample agreements, see appendices 2 and 3).

chapter

Diversion

8

Pearl Isaac, BSc Phm
Eva Janecek, BSc Phm
and Anne Kalvik, BSc Phm

DIVERSION

Some of the methadone prescribed for the treatment of opioid dependence finds its way through diversion into the illicit market. As more patients enter methadone maintenance treatment (MMT) and have access to longer periods of carry, or take-home, doses, an increase in street supplies of methadone can be expected.

The diversion of methadone should be a serious concern for pharmacists, physicians and other health care providers. Fatalities in adults ingesting diverted methadone have occurred. In non-tolerant adults, a single day's maintenance dose of methadone (50–100 mg) can be lethal (see Chapter 3).

The history of misuse of methadone, including diversion, overdose and childhood poisoning, has partially driven the introduction of guidelines — first at the federal level, followed by provincial guidelines in Ontario — regarding the maximum number of take-home doses during treatment.

Physicians may mistakenly believe that patients who are receiving take-home doses, and are diverting some or all of their methadone doses, are stable. Patients who do not take all of their take-home doses risk overdose when they consume the full prescribed dose of their medication if they come under daily observation (i.e., jail or hospital).

Some physicians and pharmacies have random callbacks for methadone take-home doses, especially for those patients who are on a high level of take-home doses (see *Methadone Maintenance Guidelines*, included with this Guide). Subsequent quantitative analysis of the returned doses is done by some programs. Many pharmacists request that patients return empty medication bottles to the pharmacy before new take-home doses are dispensed. Callback of take-home methadone and empty bottles (see above) is a way of deterring and identifying diversion. Missing or diluted take-home methadone, or missing bottles, may indicate diversion of methadone and/or containers. Urine toxicology results may, at times, indicate

the possibility of diversion by the absence of methadone or its metabolite. Finally, the way methadone is dispensed (with each daily dose dissolved in 100 mL of fruit drink) makes it less attractive than most opioids on the illicit market. The large volume and the fruit drink deter injection; the large volume also makes it difficult to retain in the mouth.

Allegations that a patient is diverting methadone may have serious consequences. Before any action is taken, the possibility that a patient is diverting methadone should always be discussed with the prescriber and counsellor (if applicable).

Pharmacy Tips to Minimize Diversion

Always:

- positively identify the patient prior to medicating by asking for photo identification or by maintaining a current photo file in the pharmacy
- dilute the methadone dose to approximately 100 mL with a suitable vehicle such as orange drink before dispensing
- carefully supervise the ingestion of methadone doses in the pharmacy
- ensure that the patient has swallowed the entire methadone dose by speaking to the patient and getting a verbal response
- counsel the patient to transport and store take-home doses securely (e.g., in a locked container in the refrigerator)
- dispense take-home doses directly to the patient, not to friends or family members
- maintain a policy of not replacing lost methadone doses (except under extreme circumstances and with physician approval)
- prevent double-dosing by confirming the amount and the time of the last dose when a patient is transferring to your pharmacy (or discharged from hospital or jail, or courtesy dosing).

Consider:

- having the patient return empty medication bottles with the labels intact before issuing new take-home doses
- refusing home deliveries except in extremely unusual circumstances and with physician approval
- recommending that the program screen the patient's urine for the presence of methadone (parent and metabolite)
- assisting the methadone prescriber to arrange temporary "guest dosing" at another pharmacy or clinic for a patient who must travel and is not suitable or stable enough for take-home doses

- offering water after ingestion of methadone
- diluting the observed dose in a larger-than-usual volume of juice (200 to 400 mL) to help ensure ingestion if methadone retention in the mouth is suspected.

chapter 9

Continuity of Care When Patients Are Institutionalized

Pearl Isaac, BSc Phm
Anne Kalvik, BSc Phm
and Eva Janecek, BSc Phm

CONTINUITY OF CARE WHEN PATIENTS ARE INSTITUTIONALIZED

When a patient in methadone maintenance treatment (MMT) is hospitalized or incarcerated, pharmacists and other health care providers of the institution must work closely with the patient's usual pharmacist to provide uninterrupted care that is optimal, safe and effective for the patient. Effective sharing of information among those who provide MMT is essential in ensuring continuity of care.

Authorized prescribers are on the staff of many hospitals and prisons. However, there are still institutions without an authorized prescriber on staff, or there may be times when the authorized physician is not available.

Many hospitals and prisons now stock methadone or have arrangements with community pharmacies to provide methadone to their institution.

At present, health care staff of Ontario's provincial correctional facilities are being encouraged to continue providing methadone to inmates who had been receiving methadone in the community. Staff of Canada's federal correctional facilities provide methadone to inmates who had been receiving MMT in the community. Inmates first diagnosed with opioid dependence upon incarceration in federal prisons are generally not started on methadone, although beginning such inmates on MMT is included in the future plans for these institutions.

Continuity of care is essential for safe and effective MMT. It is particularly important in hospital settings when patients are receiving other medical treatments. Double-dosing and missed dosing, which can occur when individuals move in and out of institutions, must be avoided. Such situations can have serious consequences, including overdose or relapse to illicit opioid use.

Communication

In order to provide seamless care, a patient's **community pharmacist** who becomes aware of a planned admission or incarceration should contact the hospital or prison pharmacy. Advance notice of the admission/incarceration allows the institutional pharmacy to make the necessary preparations — purchase methadone powder, prepare methadone stock solution, facilitate any necessary authorization, etc.

To ensure continuity of treatment and to minimize the risk of error, the institutional pharmacist receiving a MMT patient must gather certain information before dispensing methadone. The patient's usual pharmacist, prescriber and/or program staff are essential sources of much of the required information, including the following:

- What is the current methadone dose?
- When was the last dose of methadone taken by the patient/inmate? Was it this morning? Were any doses missed? (If doses were missed, the usual dose may be too high because of loss of tolerance in the interim [see Chapter 6].)
- What is the pattern of pickup (compliance)?
- Does the patient/inmate receive take-home doses? If so,
  - how many take-home doses were last dispensed?
  - when was the last take-home dose actually ingested?
  - were any take-home doses brought in by the patient/inmate?
  - are any take-home doses left at home?
- What other medications or drugs is the patient/inmate currently taking? (e.g., high doses of benzodiazepines, if stopped abruptly, could result in life-threatening withdrawal)

Gather any relevant clinical information. For instance:

- What is the condition of the patient with respect to opioids, alcohol, benzodiazepines, stimulants?
- Is the patient/inmate intoxicated?
- Is the patient/inmate in withdrawal?
- Is the patient/inmate pregnant?
- Does the patient/inmate have any other medical conditions? Any psychiatric conditions?
- Is there a need to treat pain (see Chapter 12)?
- Are there medical reasons for delaying medicating with methadone?

It is important to remember that there may be valid medical reasons for delaying medicating with methadone, even though all the above information has been gathered (e.g., patient/inmate is intoxicated or showing signs of respiratory depression).

It may also be necessary to help the attending physician at the institution to obtain a temporary authorization if there is no authorized methadone prescriber on staff.

It is important that the usual prescriber and/or clinic staff are informed of the patient's hospitalization or incarceration, as well as of the patient's status regarding the continuation of MMT.

Temporary Authorization for Physicians

Physicians and pharmacists should contact the College of Physicians and Surgeons of Ontario (CPSO) or the federal Office of Controlled Substances (OCS) to inquire about temporary authorization.

Provision of Methadone in Hospitals and Prisons

Communication

On admission, the patient's/inmate's usual pharmacist and prescriber should be made aware of the admission/incarceration.

On discharge, it is very important that the usual methadone prescriber and the community pharmacist be made aware of the date of discharge, of when the last dose was given in the institution, and of whether or not any dose changes occurred in the institution. The usual pharmacy may still have a valid prescription for this patient dating from pre-hospitalization/pre-incarceration. It is imperative that the patient not be double-dosed on the day of discharge. It is also important that the patient not miss any doses.

Orders

An authorized methadone prescriber must write and sign orders. They must be clear and specific with regard to date and dose of methadone, and adhere to institutional automatic stop order policies.

Examples of orders:
correct: methadone 70 mg po od (observed), start date _____ , end date _____ (inclusive).
incorrect: methadone 70 mg po od x duration of stay.

Preparation, Storage and Dispensing

- Methadone should be dispensed to the nursing unit in individual daily doses.
- Methadone doses should be diluted with juice (unless the nursing unit does not have a locked refrigerator or more than a couple of doses are dispensed).
- Like other narcotics, methadone should be kept at the nursing unit in a locked location (in a locked refrigerator, if possible) until it is to be administered.

Even if the patient's/inmate's own take-home doses have been brought in, it is strongly recommended to use the institution's own methadone. It is the responsibility of the institution to ensure the quality of medications administered to patients/inmates. It is always possible that the patient/inmate or someone else might have tampered with the take-home doses. Take-home doses brought in by the patient should be destroyed and their destruction clearly documented.

For more detailed information on preparation and storage, see Chapter 5.

Administration

If methadone is sent to the nursing unit undiluted, juice must be added to each dose before administration.

Methadone doses should never be left at the patient's bedside. Nurses should supervise ingestion and verify that the dose has been swallowed. Doses should be signed off on administration sheets as for other "straight" narcotics.

Procedures When Fluids Are Restricted or Prohibited

Since methadone is long-acting, the dose can be held until after the procedure, provided the procedure is brief and ends not too long after the patient's regular time of methadone ingestion.

OR

Because methadone is very water soluble, it can be prepared in a small volume and/or diluted with a very small volume of juice and given prior to the procedure, with the agreement of the anesthetist or other physicians involved. This will prevent withdrawal from developing during long or complicated procedures.

Weekend Pass

If the patient did not have take-home privileges prior to admission, the patient should generally not be provided with methadone as part of weekend pass medication. If take-home doses are under consideration, the usual methadone prescriber should be consulted regarding this issue. Take-home doses are provided after careful consideration of functional stability (see "Dispensing Take-home Doses" in Chapter 7).

Alternatives to take-home doses might be:

- daily dosing at the usual community pharmacy
- daily dosing at another pharmacy close to where the patient will be staying during the pass (see "Guest Dosing" in Chapter 7).

If the patient usually receives take-home doses, it is best to consult with the usual prescriber regarding the suitability of take-home doses at the time of arranging the weekend pass.

In each case, an authorized prescriber must write a clear order or prescription specifying the number of take-home doses or supervised doses (respectively) to be dispensed for the weekend pass.

Treatment of Pain

See Chapter 12.

Discharge/Release to the Community or Another Institution

Upon discharge/release, the institutional pharmacist should ensure continuity of MMT by communicating clearly with the pharmacist who will take over dispensing. In view of the risks of intoxication or overdose from the patient receiving the wrong dose or being double-dosed, and the risk of relapse to illicit opioid use, information that has implications for patient safety should be shared. The usual pharmacist and the patient's usual methadone prescriber and/or program staff should be informed of the following:

- that the patient/inmate is now discharged/released
- what the current methadone dose is, and whether or not any changes of dose occurred during the stay in the institution
- when the last dose was given in the institution (and whether any take-home doses were dispensed).

chapter

10

Methadone: Adverse Effects, Toxicity, Overdose and Withdrawal

Pearl Isaac, BSc Phm
Anne Kalvik, BSc Phm
and Eva Janecek, BSc Phm

METHADONE: ADVERSE EFFECTS, TOXICITY, OVERDOSE AND WITHDRAWAL

When taken daily in appropriate doses, methadone is well tolerated and is free of organ-specific toxicity. Most adverse effects are encountered at the start of methadone maintenance treatment. Adverse effects at this time may be owing to an excessive or inadequate dose of methadone. Many of the adverse effects of methadone, such as drowsiness, are usually transient and thus should not be an issue once the patient is stabilized. However, some adverse effects (e.g., constipation, sweating) may diminish more slowly or persist throughout the treatment.

Some symptoms reported by patients may be related to effects of other drugs, including alcohol, that a patient may be using. The symptoms may also be related to a concurrent psychiatric or medical condition. Pharmacists are the health professionals who see MMT patients most frequently (initially on a daily basis). They are in an ideal position to monitor the effects of methadone, to monitor the general health and well-being of their patients, and to provide the physician and other members of the treatment team with useful information.

Adverse Effects

Much myth and folklore about adverse effects of methadone exist among patients. It has been said that every possible effect and its opposite have been attributed to methadone. In reality, methadone is generally well tolerated and the adverse effects that have been associated with methadone are relatively few. Pharmacists can help patients to correctly identify adverse effects related to methadone.

The following is a list of common adverse effects:

- sedation
- sweating
- constipation
- weight changes
- psychoactive effects
- sexual problems
- insomnia
- gastrointestinal symptoms.

Sedation

Drowsiness or sleepiness may occur at the start of treatment and with increases in dosage. Patients become tolerant to this effect with continued treatment. Patients should be cautioned to avoid driving or engaging in other activities requiring alertness until they are stabilized and tolerant to this effect. Alcohol should be avoided because of additive sedation. Patients who exhibit excessive sedation should always be referred to their physician for an assessment.

Sweating

This commonly reported adverse effect might be owing to a methadone dose that is too high or too low, though some patients report that this effect persists throughout treatment. It is said to occur in up to half of cases when high doses are used. In some clients, excessive sweating may subside only with a methadone dose reduction. However, the potential benefit of a dose reduction must be balanced against the increased risk of relapse to opioid use. Patients can be reassured that while this effect is unpleasant, it causes no medical problems.

Constipation

This frequently reported adverse effect is common to all opioids, including methadone. Constipation results from opioid interference with bowel motility at the myenteric plexus, which causes poor propulsion of intestinal contents. Symptoms may diminish with time, but in some patients constipation persists throughout treatment. To minimize constipation, patients can be encouraged to increase their consumption of fruits, vegetables and other fibre. Regular exercise and increased fluid intake may also help to lessen this effect. In some cases, the physician or pharmacist may recommend occasional laxative use. Regular use of stimulant laxatives should be discouraged.

Weight Changes

Some patients in MMT complain of weight loss. However, more patients complain of weight gain. Increases in weight may be due to factors such as changes in lifestyle, better nutritional status, reduced physical activity, etc.

Psychoactive Effects

Slight but measurable mood elevation may occur at the time of peak methadone plasma levels, even after the dose has been stabilized. Mildly overmedicated patients who receive a methadone dose slightly above their established tolerance level may also experience a definite but mild "euphoria." Some patients attribute this feeling to their methadone dose and associate this state with being "normal." When these individuals no longer experience this state, they describe themselves as feeling "sick" or being "in withdrawal." However, this does not mean that most patients will seek higher doses to experience euphoria.

Sexual Problems

Some patients report altered sexual desire or impaired performance. Some experience reduced desire while others experience increased desire associated with increased stability.

Insomnia

Many patients complain of insomnia. In most cases, sleep will improve as patients are stabilized. Sleep difficulties may also be related to other causes such as depression or anxiety. Pharmacists can take the opportunity, when interacting with patients, to discuss good sleep hygiene techniques. Sleep patterns change as people get older and older adults may not need as much sleep as they once did. Patients can be advised to:

- exercise regularly and get some fresh air during the day
- avoid strenuous activity before going to bed
- avoid naps during the day
- have a warm glass of milk or a light snack before bedtime
- take a warm bath before bedtime
- avoid dwelling on your problems at night
- share worries with close friends
- make their sleeping area a comfortable, soothing place
- avoid alcohol- and caffeine-containing drinks, especially in the evening
- go to bed when tired and not before
- get up at the same time each morning
- get up if they cannot fall asleep and do something relaxing until they feel sleepy.

Adverse Effects that Occur Seldom or Rarely

Peripheral Edema

Rarely, patients report swelling of the feet and ankles shortly after starting MMT. This effect may be transient or may persist. In some patients edema resolves only when they are tapered off methadone. The risk of relapse to illicit drug use after tapering has to be weighed against the adverse consequences of edema.

Cutaneous Effects

Opioids can cause dilatation of the cutaneous blood vessels, resulting in flushing of the face and neck. Some patients also complain of itchiness, which may be due in part to the release of histamine. Allergic reactions to methadone are extremely rare and manifest as urticaria. There are reports of erythema and induration at injection sites when methadone has been injected subcutaneously.

Neuroendocrine Effects

Reported effects include the following:

- Prolactin increases (probably by reduction of the dopaminergic inhibition of its secretion).
- Suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are relatively mild and transient.
- Tolerance develops to the effects of opioids on hypothalamic releasing factors. Women whose menstrual cycles have been disrupted by their use of heroin commonly experience a return of normal cycles. With the return of usual ovulation and fertility, patients should be offered information on contraception.
- In men, circulating levels of LH and testosterone are usually in the normal range.
- No significant variations of thyroid hormones have been documented in either basal conditions or after thyrotropin-releasing hormone (TRH) stimulation; however a reduced (TSH) pituitary response has been reported in some patients.

Dental Problems

Many individuals in MMT have poor dental health. This may be owing to poor dental hygiene and/or poor dental care during problematic opioid use. Although opioids may inhibit saliva production and cause dry mouth, there is no evidence that methadone induces dental caries. While in MMT, patients should be encouraged to employ good oral hygiene practices and be referred to a dentist if necessary.

Urinary Tract

Opioid effects on the ureters and urinary bladder include an increase in tone and amplitude of contraction of the ureters. Opioids can cause inhibition of the voiding reflex. Tolerance develops rapidly to these effects. However, these effects have not been reported specifically for methadone.

An adverse effect of methadone might be partly or completely alleviated by reducing the dose. It is essential that the prescriber assess the risks, as well as the benefits of adjusting the dose. The risk of relapse to illicit opioid use resulting from reducing the methadone dose should be balanced against the benefits of reducing adverse effects.

Opioid/Methadone Intoxication and Overdose

Intoxication or overdose can result from too high a dose being prescribed, especially at the beginning of the treatment. This is the reason for initial doses of methadone between 15 and 30 mg per day. There have been several cases of overdose reported when patients are started at higher doses. Dose changes are made throughout the stabilization process, taking into account the accumulation of methadone in tissues. Given an elimination half-life of 35 +/- 12 hours, a methadone steady state will usually be reached in five to 10 days after each dose change. Accumulation must be taken into account as the dose is being increased.

Intoxication can also result from drug interactions if patients are not carefully monitored (see Chapter 11), or from patients using heroin, other opioids, alcohol or other drugs in addition to their usual dose of methadone.

Double-dosing can occur when patients move from hospital or from prison back to the usual pharmacy. By confirming the quantity and timing of the last dose (see Chapter 9), pharmacists should, to the best of their ability, ensure that clients receive the prescribed dose and are not double-medicated.

Prescribing or pharmacy errors may result in patients inadvertently getting higher doses of methadone than intended. If such error occurs, the patient should be referred to medical attention promptly.

Opioid intoxication or overdose can also result from patients using take-home doses in ways that were not intended. For example, intoxication or overdose could result from a patient on a high level of take-home doses taking more than one dose at the same time, or from a patient diverting all or part of his or her dose for a period of time and then abruptly ingesting the original dose.

Opioid intoxication or overdose can also result from patients giving away or selling part of their take-home doses to non-tolerant individuals. The lethal dose in non-tolerant adults is reported to be as low as 40 mg. Accidental intoxication or overdose that does not involve intentional diversion can also occur.

Children are particularly at risk if they accidentally ingest methadone. As little as 10 mg can be fatal to children.

Signs and Symptoms of Opioid Intoxication and Overdose

Intoxicated patients may exhibit some of the following:

- euphoria
- dysphoria
- motor retardation
- sedation
- pinpoint pupils
- slowed speech.

In addition to the above, overdose is characterized by:

- respiratory depression
- circulatory collapse
- cardiac arrest
- death

Management

It can be extremely dangerous to medicate intoxicated patients. They may be intoxicated with opioids, alcohol, benzodiazepines, other drugs or some combination of drugs. Depending on the severity of intoxication, pharmacists should use their clinical judgment either to delay medicating, to refer intoxicated patients to their physicians for medical assessment, or to refer patients to the nearest emergency department. Untreated overdose can result in death due to respiratory depression. In hospital, opioid overdose can be reversed by administering an opioid antagonist, such as naloxone, parenterally by repeated intravenous injections or infusion. Due to methadone's long half-life, naloxone be continued for much longer periods than for overdose due to other opioids. See Appendix 6.

The seriousness of methadone intoxication/overdose and its possible consequences cannot be overemphasized. For non-tolerant adults, a single day's maintenance dose of methadone (50–100 mg) can be lethal. For those beginning MMT, starting doses of 40 mg have lead to deaths after three days of treatment. The lethal dose is less if it is taken together with other opioids, alcohol, benzodiazepines or barbiturates. Children may overdose if they mistake the medication for a drink. A 10 to 20 mg dose of methadone can be fatal to a child.

Opioid/Methadone Withdrawal

Signs and Symptoms of Opioid Withdrawal

OBJECTIVE

- *nausea, vomiting*
- *diarrhea*
- *runny nose, sneezing*
- *lacrimation*
- *dilated pupils*
- *gooseflesh*
- *tremor*
- *feelings of hot and cold*
- *yawning*
- *tachycardia*
- *blood pressure elevation*

SUBJECTIVE

- *anxiety*
- *restlessness*
- *abdominal pain and cramps*
- *muscle aches*
- *bone pain*
- *anorexia*
- *craving*
- *insomnia*

The signs and symptoms associated with too low a dose of methadone are less dramatic and more subtle in nature. Patients may feel that the dose is not "holding" them. Good communication between the physician, pharmacist and patients can help the prescribing physician adjust the dose.

With abrupt discontinuation of methadone, signs of withdrawal are not usually observed until 36 to 48 hours after the last dose. Withdrawal signs and symptoms appear gradually and peak at about 72 hours after the last methadone dose. They may continue at this level for about two weeks. The withdrawal syndrome then declines very gradually. Symptoms may be experienced for months (see Chapter 6).

chapter

Drug Interactions

11

Eva Janecek, BSc Phm
Pearl Isaac, BSc Phm
and Anne Kalvik, BSc Phm

DRUG INTERACTIONS

Pharmacists should carefully monitor patients after they start or discontinue medications that may interact with methadone. *The risk of interactions need not preclude the use of any medications that can interact with methadone, except those that are contraindicated.*

Pharmacodynamic Interactions

Additive

These interactions include potentiation of CNS depressant effects, constipation and nausea. If methadone is combined with a drug that has a similar adverse drug reaction profile, the adverse effects may be additive. For example, the CNS depressant effects of alcohol and benzodiazepines are additive with those of methadone. This is particularly significant at the beginning of methadone treatment and each time the dose is changed. As tolerance to the sedative effects of methadone develops, the interaction is less pronounced. Tolerance to some effects, such as respiratory depression develops very slowly and only partially; thus additive effects of high doses of methadone and another CNS depressant may cause serious consequences. Another example is anticholinergics or medications with anticholinergic effects, which increase the risk of constipation. Severe constipation can lead to paralytic ileus (USP DI, 1998).

Antagonist

A mixed agonist/antagonist, a partial agonist or a pure antagonist will precipitate withdrawal if given to a patient receiving methadone.

Pharmacokinetic Interactions

These interactions are mainly due to alterations of hepatic metabolism, and to a lesser extent, to changes in urinary clearance. Methadone is metabolized in the liver predominantly by the cytochrome P450 (CYP3A4) enzyme (Bertz & Granneman,

1997) to inactive metabolites. Medications affecting the CYP3A4 system, or medications that are also metabolized by CYP3A4, can be expected to interact with methadone. Methadone has also been reported to be metabolized by CYP2C9 and to inhibit CYP2D6, but the clinical significance of these findings is minimal. As the knowledge of the P450 enzyme system is rapidly expanding, so is information on interactions. Some information is of a theoretical nature, whereas other information is based on case reports or clinical studies. Care should be taken when applying theoretical drug interaction information to clinical practice.

When evaluating a drug interaction, the following require consideration:

- Is medication "X" added to methadone? (*Scenario one*)
- Is methadone added to medication "X"? (*Scenario two*)
- Has the patient been receiving methadone and medication "X," and is methadone discontinued? (*Scenario three*)
- Has the patient been receiving methadone and medication "X," and is medication "X" discontinued? (*Scenario four*)

Careful monitoring cannot be overemphasized for patients starting or discontinuing medications that are potentially interactive.

The following four scenarios illustrate the importance of time sequence in evaluating the outcomes of a methadone-drug interaction:
Carbamazepine is a CYP3A4 inducer and increases hepatic metabolism of methadone.

Scenario one
A patient has been receiving the same dose of methadone for two years. After one week of receiving carbamazepine, the patient complains of opioid withdrawal. The methadone dose should be increased slowly until opioid withdrawal symptoms disappear.

Scenario two
A patient who has been on carbamazepine for three years is started on methadone. No action is required. The final methadone dose will be determined based on the patient's clinical response. Any increase in methadone metabolism induced by carbamazepine will thus be accommodated.

Scenario three

A patient has been on stable doses of methadone and carbamazepine for one year. Methadone is discontinued and there are no consequences. Carbamazepine induces methadone metabolism; methadone does not induce carbamazepine metabolism.

Scenario four

A patient has been on stable doses of methadone and carbamazepine for one year. Carbamazepine is discontinued. The patient must be monitored closely for methadone toxicity. If symptoms of intoxication appear, the methadone dose should gradually be reduced until symptoms disappear.

Other factors that require consideration are:

- compliance
- use of other drugs.

If the patient is taking either of the potentially interacting drugs sporadically, the interpretation of medication-related symptoms will be different and more difficult than in a compliant individual.

Similarly, the use of other drugs will influence the overall presentation. For example, a patient has been on stable doses of methadone and carbamazepine for a year and has been compliant with the use of both medications. The patient relapses to illicit opioid use. Then the supply of illicit opioids runs out and, as a result, the patient complains of withdrawal symptoms. The symptoms are not the result of a methadone-carbamazepine interaction.

Medications That Are Contraindicated Because They Can Precipitate Withdrawal

Naltrexone (USP DI, 1998)

- Opioid antagonist; will precipitate opioid withdrawal in methadone-maintained patients, even if prescribed for alcohol dependence.

Pentazocine/Nalbuphine/Butorphanol (USP DI, 1998)

- Mixed agonist/antagonists and partial agonists may precipitate withdrawal symptoms in methadone-maintained patients.

Medications That Can Decrease Plasma Levels of Methadone

Ascorbic acid (Vitamin C) (USP DI, 1998)

- In doses high enough to acidify urine may lead to a decrease in renal reabsorption and may result in a reduction of methadone half-life.

Barbiturates (Bertz & Granneman, 1997; Hansten & Horn, 1999)

- Induce CYP3A4.
- May precipitate methadone withdrawal symptoms if started after the methadone dose has been stabilized.
- May precipitate opioid intoxication when discontinued.

Carbamazepine (Bertz & Granneman, 1997; Hansten & Horn, 1999; Spina et al. 1997)

- Induces CYP3A4.
- Initiation may necessitate an increase in methadone dose.
- Discontinuation may necessitate a decrease in methadone dose.
- Valproic acid appears not to interact with methadone and may be a suitable alternative to carbamazepine in some patients (Quinn et al., 1997).

Efavirenz (Abramowicz, 1998)

- Induces CYP3A4.
- Theoretically may decrease levels of methadone (no clinical reports available).

Ethanol (Quinn et al., 1997)

- Chronic use can enhance hepatic metabolism of methadone through enzyme induction.
- Heavy users may experience opioid withdrawal after prolonged drinking.

Nevirapine

- Induces CYP3A4 (Glaxo, 1998).
- Cases of methadone withdrawal have been reported (Otero et al., 1999).

Phenytoin (Bertz & Granneman, 1997, Hansten & Horn, 1999; Nation et al., 1990)

- Induces CYP3A4.
- Is best avoided in MMT patients; if phenytoin is used, the dose of methadone may need to be increased when phenytoin therapy begins and decreased when phenytoin is discontinued.

Rifampin (Bertz & Granneman, 1997; Hansten & Horn, 1999; Baciewicz et al., 1987)

- Induces CYP3A4.
- May precipitate opioid withdrawal when added to methadone; may precipitate opioid intoxication when discontinued; no interaction observed with **Rifabutin**. (Bertz & Granneman, 1997; Hansten & Horn, 1999; Baciewicz et al., 1987; Brown et al., 1996).

Risperidone (Wines & Weiss, 1999)

- Methadone withdrawal symptoms reported in two cases.

Medications That Can Increase Plasma Levels of Methadone

Amitriptyline (Cantor, 1979)

- Reports of patients in MMT using amitriptyline to enhance psychoactive effects of methadone; amitriptyline may increase methadone levels.

Cimetidine (Payte & Zweben, 1998; Charuvastra et al., 1997)

- Increases methadone levels; clinical significance unknown.

Diazepam (Quinn et al., 1997; Wesson et al., 1997)

- Metabolized by CYP3A4.
- Reports of psychoactive effects similar to those produced by short-acting opioids when taken shortly before or after methadone (Quinn et al., 1997; Wesson et al., 1997).

Disulfiram (Tong et al., 1980)

- May decrease methadone metabolism; not clinically significant (Tong et al., 1980).

Erythromycin (Quinn et al., 1997; Young et al., 1996)

- Inhibits CYP3A4.
- Theoretically may increase methadone levels.

Ethanol (Quinn et al., 1997)

- Acute high blood alcohol concentrations reduce methadone metabolism by competing for metabolic enzyme activity (Quinn et al., 1997).

Fluconazole (Young et al., 1996; Tseng & Forsz, 1997; Cobb et al., 1998)

- May inhibit hepatic methadone metabolism; clinical significance unclear.

Fluoxetine

- No adverse consequences reported in a study of 44 methadone maintenance treatment (MMT) patients initiated on fluoxetine (Petrakis et al., 1998).
- Moderate increase in methadone plasma levels observed in a study of nine patients (Bertschy, 1996).
- Unlikely to have clinical consequences.

Fluvoxamine (Young et al., 1996; Bertschy, 1994)

- Has been shown to increase methadone plasma levels in one study; clinical significance unknown.
- Monitor for evidence of excessive methadone effect (Hansten & Horn, 1999).

Indinavir (Antoniou, 1998; Iribarne et al., 1998)

- Inhibits CYP3A4; clinical reports not available.

Ketoconazole (Bertz & Granneman, 1997; Hansten & Horn, 1999; Young et al., 1996)

- A potent CYP3A4 inhibitor (Medical Letter on Drugs and Therapeutics, 1999).
- May decrease methadone metabolism.

Nefazodone (Young et al., 1996; Butler, 1998)

- Potent inhibitor of CYP3A4.
- No clinical reports available.

Nelfinavir (Antoniou, 1998)

- Inhibits CYP3A4.
- No clinical reports available.

Ritonavir

- Has a high affinity for CYP3A and a lesser affinity for CYP2D6 and CYP2C9 (Iribarne et al., 1998).
- Reported to inhibit CYP3A4 (Abbott Laboratories, 1999).
- Theoretically can decrease methadone metabolism.

Saquinavir (Antoniou, 1998; Iribarne, 1998; Hoffman-LaRoche Ltd., 1998)

- Weak inhibitor of CYP3A4.
- Theoretically may increase methadone levels (clinical significance unknown).

Urinary Alkalizers

- Theoretically may increase renal re-absorption of methadone.

Other Interactions

Desipramine (Maany et al., 1989)

- Increase in plasma concentration of desipramine in patients on methadone, possibly due to reduced hydroxylation of desipramine. Monitoring of plasma levels of desipramine is recommended to prevent desipramine toxicity.

MAOIs (Hansten & Horn, 1999; Gillis et al., 1999)

- No reports of interactions with methadone.
- MAOI with concomitant use of meperidine resulted in death.
- Morphine-MAOI interactions have been less severe than have meperidine-MAOIs.
- Use extreme caution, or avoid combining MAOI and opioids.

Nifedipine (Iribarne et al., 1997)

- Methadone can inhibit oxidation of nifedipine, which may result in greater-than-expected effects or nifedipine toxicity.

Zidovudine (AZT) (Quinn et al., 1997; McCance-Katz et al., 1998)

- Methadone reduces metabolism of zidovudine and may increase its metabolite (3'-amino-3'-deoxythymidine), thought to produce anemia.
- Zidovudine toxicity and onset of anemia should be closely monitored; zidovudine dose may have to be adjusted.

Interactions with Food

Grapefruit juice (Hansten & Horn, 1999; Young et al., 1996)

- Inhibits CYP3A4.
- May result in decrease in methadone metabolism.
- Clinical significance unknown.
- No evidence that orange juice causes the same effect.

The risk of interactions need not preclude the use of any medication that can interact with methadone, except those that are contraindicated. However, patients must be monitored more closely and doses may have to be adjusted as appropriate.

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chapter

12

Methadone Maintenance under Special Circumstances

Pearl Isaac, BSc Phm
Anne Kalvik, BSc Phm
and Eva Janecek, BSc Phm

METHADONE MAINTENANCE UNDER SPECIAL CIRCUMSTANCES

Pregnant Patients

Pregnancy in a woman addicted to heroin and other opioids is frequently an indication for methadone maintenance treatment (MMT). MMT offers better outcomes for the mother and baby than continued use of heroin or other opioids. The goal of MMT during pregnancy, as in other situations, is to maintain the patient on the minimum dose required for comfort while maintaining abstinence from illicit opioids.

Methadone readily crosses the placenta, but the benefits associated with MMT far outweigh risks to the baby. Continued heroin use is associated with:

- cycles of intoxication and withdrawal detrimental to both mother and baby
- increased risk of spontaneous abortion, miscarriage and premature labour
- risk of transmitting viral hepatitis or HIV to the baby.

The benefits of MMT include:

- improved gestational age
- increased birthweight
- decreased infant mortality.

MMT provides the opportunity for the provision of improved prenatal care, including:

- medical care
- nutritional counselling

- provision of parenting skills
- psychosocial counselling.

Ideally, initial stabilization occurs in hospital, where the patient can be more easily monitored for withdrawal and fetal distress. However, patients can be stabilized on an outpatient basis (see Chapter 6 for details about dosing).

Methadone dose should be monitored carefully during pregnancy. It is important that pregnant women not miss a methadone dose. In the last trimester some patients may require twice-daily dosing or an increase in their dose (see Chapter 6).

Women are encouraged to remain in MMT throughout their pregnancy. Women who wish to discontinue MMT may consider this option during the second trimester. However, discontinuation must be carried out very carefully under the supervision of an experienced physician (see Chapter 6 for details about dosing).

If the patient's partner is abusing and/or addicted to opioids, that partner or spouse is also encouraged to seek treatment. Treatment of the partner or spouse provides better support to the mother and helps to prepare a good home environment for the child.

Babies born to mothers in MMT frequently experience neonatal abstinence syndrome. This can easily be treated by experienced clinicians in a high-risk nursery. Withdrawal symptoms are evaluated according to a scoring chart and are usually treated by administering oral morphine solution.

Breastfeeding

Breastfeeding by mothers in MMT is encouraged to facilitate bonding with babies. For patients on doses over 50 mg, decisions regarding breastfeeding are made on an individual basis. Methadone enters the breast milk in small quantities. Levels of methadone in breast milk peak two to four hours after dosing and, if possible, nursing should be avoided during this period. As babies grow and consume larger amounts of breast milk (at three to six months), it is suggested that they be weaned.

Breastfeeding is contraindicated if the patient is HIV positive.

It is very important that breastfeeding mothers avoid the non-medical use of drugs (e.g., alcohol, cocaine, heroin, nicotine, etc.). The compatibility of breastfeeding with other medications taken by mothers should be considered as well.

Patients with HIV/AIDS

Individuals who are using psychoactive substances may have difficulty complying with HIV medication regimens. MMT may aid compliance by helping the patient develop functional stability. Since the pharmacist sees the MMT patient more frequently than other health professionals involved in MMT, the pharmacist can use this frequent contact to promote compliance with HIV medications.

From a public health point of view, compliance with MMT helps to decrease the transmission of HIV infection.

The potential for drug interactions should not preclude the use of methadone in patients on HIV medications (see also Chapter 11).

Treatment of Acute Pain in Methadone Maintenance Treatment Patients

Patients in MMT may require pain relief. These patients are largely tolerant to the analgesic effects of methadone, even though tolerance generally does not develop to methadone's effectiveness in preventing the onset of opioid withdrawal and opioid craving.

When pain is present, the usual methadone maintenance dose should be continued. This is considered a baseline for preventing the emergence of withdrawal and craving. It will not provide significant pain relief.

Patients' need for analgesia should be met with adequate treatment, as for any patients in pain. For mild to moderate pain, non-opioids such as acetaminophen or non-steroidal anti-inflammatory drugs may be useful. Non-pharmacological treatments should also be considered. For moderate to severe pain, it may be appropriate to use opioid analgesics in doses similar to those used for other individuals with similar pain. There is evidence that some methadone-maintained patients have a lower tolerance to pain and may require larger doses or more frequent dosing. Frequent assessment of patients' condition is recommended. Care should be taken to recognize drug-seeking behaviours.

When an opioid is required, only pure agonists should be used. Partial opioid agonists or agonist-antagonists, such as pentazocine (Talwin®), butorphanol (Stadol NS®) and nalbuphine (Nubain®), should never be used. Such drugs can precipitate withdrawal symptoms. Patients who require an opioid prescription from a physician other than the methadone prescriber should allow open communication between

prescribers to ensure safe and effective MMT and to avoid being suspected of double-doctoring.

If patients in MMT receive a prescription for another opioid analgesic, they must disclose to the prescribing physician/surgeon/dentist that they are receiving methadone. Failure to disclose this information under these circumstances is considered to be a legal offence (commonly called "double-doctoring"). In addition to the legal implications, there are the health implications (possible opioid withdrawal, possible opioid intoxication/overdose) of taking additional opioids. Pharmacists who suspect double-doctoring should bring it to the attention of the treating health professionals.

See also "The Treatment of Pain in the Context of Illicit Opioid Use and Methadone Maintenance Treatment" in Chapter 2.

Disruptive Behaviour by Patients

Prevention

Pharmacy staff should create a respectful environment for all their patients, including patients on methadone. Judgmental or other negative attitudes only reinforce the stigmatization of methadone and MMT patients. These attitudes cannot help but be conveyed to methadone patients and may hinder patient progress. Staff should be honest, supportive and respectful in their interactions with patients in MMT. Patient complaints of not being treated in a dignified and respectful manner should be taken seriously.

It is important for the pharmacist to discuss expectations with each new patient at the start of treatment. Often difficulties can be prevented by having a written or a verbal agreement. Such an agreement can include statements that the patient can expect professional, fair and courteous treatment by the staff at the pharmacy. The pharmacy staff can also expect the same respect from the patient. The agreement can also include explicit statements, such as:

- no verbal or physical threats
- no violent behaviour
- no shoplifting
- no drug using or drug dealing
- prompt arrival for medicating
- prompt payment for medication
- no loitering in the store.

Termination of Methadone Dispensing

If the patient fails to meet agreed-upon expectations, the patient may be advised to go to another pharmacy. However, the availability of pharmacies that dispense methadone may be limited in some communities.

If the pharmacist decides to end the provision of pharmacy services to a MMT patient, he or she must ensure that the decision is clearly communicated to the patient. If possible, communicate the decision to the patient in writing and send a copy to the methadone prescriber. If possible, the patient should be given a reasonable amount of time to make alternative arrangements and assisted in identifying another pharmacy that dispenses methadone (the Ontario College of Pharmacists [OCP] may assist in this regard).

The pharmacist should advise the pharmacy staff of the decision and the alternative plans. Also, the patient's methadone prescriber and/or the program need to be informed of the decision the date dispensing will stop and the reasons methadone dispensing to the patient was terminated (also see Appendix 7, "Ending the Pharmacist/Patient Relationship").

APPENDICES

METHADONE MAINTENANCE THERAPY: INFORMATION FOR CLIENTS*

What is methadone?

Methadone is a long-acting opioid, or narcotic, medication. It's an effective and legal substitute for heroin or other narcotics that you have been using.

Methadone helps to stabilize the lives of people who are dependent on heroin, and to reduce the harm related to drug use. Methadone has been used in treatment programs since the mid-1960s.

How is methadone taken?

Your doctor will provide the pharmacy with a prescription for your methadone. This prescription must be renewed periodically by your doctor. He or she will determine how often you come for appointments, depending on your needs and progress.

Methadone is a medication that is taken orally. It is diluted with juice such as orange juice. When you first start on methadone, you will be asked to go to your pharmacy each day to drink the medication. As you progress in your treatment, you may be eligible to take home some doses. These are called "carries."

Your carries must be stored safely to make sure the medication is not taken by anyone else, especially a child. Carries should be refrigerated.

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How does methadone work?

Methadone is part of a long-term maintenance treatment for narcotic- or heroin-dependent people.

At first, the goal is to stabilize you by improving your general sense of well-being by preventing physical withdrawal. Methadone will significantly diminish your drug cravings, and help you reduce or eliminate heroin use.

The effects of methadone last for one to two days, so you can stop taking heroin or other narcotics that you may have been using many times a day. You can then devote your time to improving your life.

Methadone is a long-acting medication. So when your dose is adjusted, it may take four or five days for you to experience the full effect of the dose change. Be patient.

Treatment works best when combined with other services. Some services you may want to explore are relapse prevention, individual or group counselling and case management. Case management includes crisis intervention, as well as help for social problems concerning housing or food, and legal or financial concerns.

Remember, the goal of treatment is to stabilize your body physically so that you can make the best of your life.

How long do I have to stay on methadone?

This is the most common question we're asked. Even after about 30 years of experience with methadone, we still don't have an answer that applies to everyone. What we can say is that most people who are successful coming off methadone show three important characteristics:

- First, their lives have been stabilized after they've been on methadone maintenance treatment for more than a year.
- Second, the decision to stop taking methadone is made with their doctor, who gradually decreases the dose while providing support.
- Finally, they've made changes in their lives that show they're stable. For example, they may have a stable family life, support from the non-drug-using community, steady employment and fewer financial or legal difficulties.

It's important to understand that methadone, when taken as prescribed, is a safe and effective medication that individuals can take for years. We encourage you to use it for as long as you feel it's working for you, and there are no medical concerns.

Does methadone have any side-effects?

Once your dose is stabilized, methadone is usually a very well-tolerated medication. Most people experience few, if any, side-effects. Some may experience some of the following symptoms at some time. While this may be distressing, these symptoms are rarely dangerous and most diminish with time. Please let your physician or pharmacist know if any of these symptoms are bothering you:

- **Sweating.** This can be due to a methadone dose that is too high or too low.
- **Constipation.** You can try increasing fibre (such as bran) in your diet if you experience this problem. Regular exercise and drinking more fluids may also help.
- **Sexual difficulties.** Some people experience reduced desire, while others show an increased desire associated with a better life.
- **Sleepiness or drowsiness.** This is common, and may be caused by too much methadone. You should be assessed by your doctor to see if your dose needs to be adjusted. Don't drive a car or participate in activities that require you to be alert while this is a problem.
- **Weight change.** People sometimes put on weight, but this may be because they're now eating properly and are healthier.

Can methadone interact with other drugs?

Remember that methadone is a medication that may interact with other medications you may be taking. Alcohol, as well as prescription, non-prescription, herbal and street drugs may interfere with the action of methadone. Discuss all medications you are taking with your pharmacist or doctor.

Is methadone dangerous?

When methadone is prescribed to a narcotic-dependent person at a proper dose, and is monitored by a doctor, it is a safe medication.

However, it can be extremely dangerous if used inappropriately. Methadone should never be taken by individuals for whom it is not prescribed. It can cause overdose and death when a person who is not dependent on narcotics takes it. Children are particularly at risk for overdose and death if they swallow methadone accidentally. If this happens, seek emergency treatment immediately.

What are my responsibilities?

It is your responsibility to drink your methadone dose every day. If you have carries, you must make sure that you store your methadone safely until you drink it. It's best to refrigerate your carries.

Also, you must not give or sell part or all of your dose to anyone. Diverting your methadone is a serious program violation and will result in loss of carries. If there are further incidents of diversion, you could be withdrawn from the methadone maintenance program.

Will methadone cure me?

There is still no "cure" for drug dependence, or addiction. What your participation in a methadone treatment program can do is to make your life more stable, allow you the opportunity to make positive lifestyle changes and provide you with an environment that supports you.

Remember, you are the one making the changes. We are here to support you in whatever way you feel will help improve the quality of your life.

Methadone is a long-acting opioid, or narcotic, medication.

It's an effective and legal substitute for heroin or other narcotics that you've been using.

Prepared by Pharmacy Services & the Opiate Clinic
Centre for Addiction and Mental Health
33 Russell Street
Toronto, ON M5S 2S1

SAMPLE METHADONE MAINTENANCE TREATMENT AGREEMENT

Client Name: _____ File No.: _____

Methadone Treatment Agreement

I _____ agree to enter into a program of methadone maintenance treatment offered by [NAME OF YOUR PROGRAM]. This treatment program is specifically designed to help me deal with my problems of opiate dependence, and will assist me in dealing with the psychological and social difficulties that often accompany problems of addiction. The main purpose of this program is to help me make positive changes in my life related to my use of opiates and other substances.

I am seeking help with reducing or stopping harmful use of illicit drugs and of substances like alcohol and prescription drugs. I am interested in gaining assistance in overcoming my problems with drug use and any associated psychosocial difficulties.

I understand that [NAME OF YOUR PROGRAM] offers a range of services in conjunction with methadone maintenance treatment, which can assist me in achieving my goals. Medical care pertinent to my methadone treatment will be provided. In addition, a range of counselling services are encouraged and available on a voluntary basis. Counselling options include support groups, relapse prevention groups, individual counselling, crisis support and assistance with addressing any specific concrete needs that I have, such as financing, housing, and referrals to other community services.

I understand that this treatment is likely to help me, but I cannot be guaranteed that the treatment will work in my individual case. If treatment is not proving effective, other clinical care will be discussed with me.

I understand that, as a participant in this treatment program, I am agreeing to the following:

1. Methadone Treatment

Methadone is an opioid and, as such, its prescribing and dispensing are regulated by a number of legal guidelines. I understand that my receipt of methadone depends upon the following:

- I agree to pick up my medication during pharmacy dispensing hours and to take the medicine according to the pharmacist's directions. Dispensing hours are clearly posted.
- I agree to notify program staff of all prescription and non-prescription medications that I am taking. I will bring my prescriptions or medication bottles to the pharmacy so that the exact drug and dosage can be noted. The treatment team will advise me, in consultation with my prescribing physician, of any drugs that I am taking that are inconsistent with my treatment plan. I will then refrain from taking these drugs while I am receiving treatment on this program.
- I understand that on some days I may be required to leave a supervised urine sample before obtaining my methadone dose. If I am unable to provide the required sample, staff may ask me to wait. Upon providing the urine sample, I will receive a medication slip that I can take to the pharmacy to pick up my methadone. I understand that tampering with urine samples is a serious program violation.
- I understand that, as I progress in the program, I may request methadone carries or community pharmacy pickups, which reduce the number of days I have to attend the clinic.
- I understand that I may request to have my methadone dose reduced or increased at any time by discussing this with my physician.

(continued on next page)

Sample Methadone Maintenance Treatment Agreement (continued)

- Methadone is prescribed for my personal use only, and I will use it as prescribed. I will present a picture identification card to the pharmacy staff when I pick up my methadone dose. Sharing, selling or distributing methadone is illegal and considered a serious program violation.
- When I work to improve my situation, I realize that achieving lasting change is challenging. To help me keep on track with my targeted goals, I am aware that the treatment team will provide checks to ensure that I am taking my methadone and that I am providing my own urine samples.

2. Initial Assessment/Treatment Progress Reviews

- I understand that, upon entry to the program, I will receive an initial comprehensive assessment that will be used to help me develop a personal action plan based on my specific needs and goals. In the event that I am unable to attend the scheduled initial assessment meetings, I will notify the program's staff as soon as possible, preferably at least 24 hours in advance. Program staff will demonstrate the same courtesy if they are unable to attend a scheduled session.
- I will be offered a range of counselling options that I can elect to engage in. I understand that continued eligibility in most counselling services depends on regular attendance.
- I understand that I will be expected to attend periodic meetings (once every three months during the first year on the program) to review my treatment progress.

3. Medical Care

- I will be provided with an initial assessment by my physician affiliated with the program. This assessment is for the purpose of determining if methadone is appropriate and safe for me. I agree to be reassessed by a program physician at least annually for continuance in methadone maintenance treatment.
- I understand that [NAME OF YOUR PROGRAM] is a specialized addictions service and not a family practice clinic. It is my responsibility to have a family physician in the community. I agree to sign a consent form allowing my family physician and the clinic staff to exchange medical information relevant to my care. A copy of this form will be sent to my family physician. I understand that if I do not have a family physician, the clinic staff will assist me in finding one.
- If another physician or dentist proposes to prescribe opioids (i.e., narcotics) for me, I will inform him or her that I am receiving methadone. Obtaining narcotic medications from more than one physician or dentist could be dangerous to my health and is illegal.

4. Clinic Environment

- I understand that the clinic is committed to maintaining an environment that is safe for clients, visitors and staff, and to maintaining positive, respectful behaviour between people, which does not include threats, violence or destructive behaviour. I agree to uphold these standards.
- I understand that if I have any concerns, I may approach staff immediately. If I am not satisfied with the response I receive, I understand that there is a problem resolution procedure.

5. Confidentiality

- My privacy will be respected. Confidentiality of my health record will be protected in the same way that it is in other health facilities. No release of information from my health record will be given without my written consent or as required by law.
- I understand that in certain situations the treatment team may be required by law to give out information without my consent. This involves situations where the treatment team perceives my behaviour to be a potential risk to myself or to other people (such as when child neglect or abuse is suspected).
- Because my participation in the program will bring me into contact with other opiate users, I expect other clients to be respectful of my rights, confidentiality and treatment goals. I will in turn respect the rights, confidentiality and treatment goals of other clients.

My signature below indicates that I have discussed this treatment agreement with my treatment provider and understand and agree to all of the above. Should I fail to meet my responsibilities as a participant in this program, I understand that this will result in a reassessment of the treatment plan and a consideration of my continued involvement in the program.

I have been informed about methadone and have had an opportunity to ask questions and have my questions answered. I understand that I can ask the pharmacy at any time about methadone or other medications.

Signature of Client _____ Date _____

Signature of Treatment Provider _____ Date _____

SAMPLE METHADONE CARRY AGREEMENT

I understand that the methadone I am receiving is for my consumption only.

I undertake full responsibility for making sure this methadone does not get into anyone else's hands.

I understand that while this dose of methadone is safe for me, it can cause serious overdose and possibly death in another person.

I have been counselled about appropriate storage.

I will consume the methadone on the dates specified on the medication label.

I agree to return all empty methadone bottles on the day following each carry period.

Client's signature: _____ Date: _____

Pharmacist's signature: _____

SAMPLE REMINDER ABOUT METHADONE CARRIES

The methadone you are receiving is:

- for your consumption only
- for use on the day specified on the label.

It is your responsibility to make sure this methadone does not get into anyone else's hands. While the dose of methadone is safe for you, it can cause serious overdose and possibly death in another person. Children are particularly at risk for overdose, and as little as 10 mg can be fatal. If a child or anyone else accidentally swallows methadone, seek emergency treatment **immediately** by calling 911.

MAKE SURE YOU STORE YOUR METHADONE SAFELY.

A locked box for your carries is recommended.

Remember to bring your empty carry bottles to the pharmacy on your next scheduled day.

SAMPLE METHADONE PRESCRIPTION FORM

Centre for Addiction and Mental Health
Centre de toxicomanie et de santé mentale

Centre for Addiction and Mental Health
33 Russell Street, Toronto, Ontario
Canada M5S 2S1
Telephone (416) 535 8501 ext. 6019
Fax (416) 595 6606

Centre de toxicomanie et santé mentale
33, rue Russell, Toronto, Ontario
Canada M5S 2S1
Telephone (416) 535 8501 ext. 6019
Fax (416) 595 6606

Valid only at:

☐ CAMH - ARF

☐ Pharmacy (specify):

_____

_____

_____

Methadone Prescription Form

Name | *Date* | *File #*

Rx *Methadone* _____ *mg* _____
p.o. dispensed daily mixed in orange drink. *Dose in words*

Start Date: _____ *End Date:* _____ *Inclusive*

Drink observed in the pharmacy on days circled:

Mon *Tue* *Wed* *Thur* *Fri* *Sat* *Sun*

The following doses are to be dispensed as take home doses:

Mon *Tue* *Wed* *Thur* *Fri* *Sat* *Sun*

Special Instructions:

Contact prescriber before filling this prescription if dose is increased by more than 15mg., unless noted above.
Hold prescription if more than three consecutive doses are missed, and contact prescriber.
Notify the CAMH-ARF pharmacy (416) 595-6014, fax (416) 595-6606, if a dose is missed.
Fax a copy of this prescription to the CAMH-ARF pharmacy if there are any concerns about this prescription.

_____ _____ *M.D.*
Signature *Print Name*

Prepared by	*Date*	*Dispensed by*

Peter Selby MBBS,CCFP,
Eva Janecek, BSc Phm

MANAGEMENT OF METHADONE OVERDOSE: AN OVERVIEW

Methadone Overdose

Methadone overdose is characterized by prolonged central nervous system and respiratory system depression and pinpoint pupils with variable levels of hypoxia, hypotension, shock, gastric hypomotility and ileus. Non-cardiogenic pulmonary edema (NCPE) and Adult Respiratory Distress Syndome (ARDS) (Drudi et al., 1997) have also been reported.

Methadone overdose can occur under the following circumstances:

Accidental Ingestion

This usually occurs in children (Aronow et al., 1972; Lorenzo & Weinstock, 1995; Binchy et al., 1994) because they mistake the methadone for an orange juice drink. Also, only 50 per cent of methadone-treated patients store their medication in a safe place (Calman et al., 1996). Pharmacies are not required by law to dispense methadone in childproof containers, although it is strongly recommended.

Intentional Ingestion

This can occur when non-tolerant individuals procure diverted methadone either to experience euphoria or to mitigate withdrawal symptoms because they were unable to procure heroin.

Iatrogenic Overdose

This can occur owing to inappropriate prescribing or inadequate monitoring of patients admitted to methadone treatment programs:

Early in treatment (during the induction phase)

This can occur during initiation of treatment if the patient is prescribed a starting dose greater than 15 to 30 mg or the dose is increased rapidly, leading to accumulation with subsequent toxicity and death (Caplehorn, 1998).

Late in treatment (during the maintenance phase):
This can occur when a patient taking a stable dose of methadone gradually tapers the dose down without informing the physician and diverts the remainder of the medication. If the patient is then required to drink the methadone daily under observation (e.g., because of admission to hospital, loss of take-home doses or incarceration), toxicity may ensue owing to the interim loss of tolerance to the prescribed dose.

When a patient prescribed a dose greater than 50 mg skips three or more days of medication and then resumes at the same high dose, the patient is likely to overdose owing to loss of tolerance.

Clinical Findings

General Condition

The overdosed patient may initially be alert and awake but will gradually become drowsy and comatose with ensuing cyanosis and eventual respiratory arrest if the condition is not diagnosed. There may not be evidence of needle track marks, since in Canada most methadone is taken orally. The presentation could be atypical if the patient has taken other drugs like cocaine, alcohol or benzodiazepines.

Vital Signs

The respiratory rate is usually slow (i.e., less than 10 to 12/min.) and shallow. Hypotension may be present secondary to apnea.

Head and Neck Examination

The pupils will be pinpoint but mydriasis may occur if severe hypoxia occurs secondary to prolonged respiratory acidosis. The presence of pink froth at the mouth/nose should alert the physician to the possibility of NCPE.

Respiratory System

Hypoventilation: Respiratory depression may be delayed by up to six hours after ingestion (Geller & Garretson, 1994). Prolonged respiratory depression may occur up to 65 hours after ingestion (Sey et al. 1971; Gayle et al., 1991; Romac, 1986; Hendra et al., 1996). Pulmonary edema may be present (Frand et al. 1972; Zyroff et al. 1974). The onset can be within 24 to 72 hours after the overdose. It is thought to be secondary to hypoxia caused by an increase in pulmonary vascular pressure and increased permeability of pulmonary tissue. It is usually reversible with appropriate treatment without long-term sequelae.

Cardiovascular System

One case-control study found that 66 per cent of patients maintained on methadone who continued to abuse other drugs or alcohol had some ECG abnormalities as compared with 12.5 per cent of controls (Lipski et al., 1973). One-third of these had prolonged QTc, one-third had prominent U waves and another third had bradyarrhythmia. Arrhythmias are not usually associated with methadone overdose. However, reversal of intoxication with naloxone may precipitate arrythmias in patients with underlying heart disease, especially in those with concomitant cocaine or alcohol use (Cuss et al., 1984) or in those in the early post-operative phase (Gilman, 1982).

Central Nervous System

Lethargy, coma and miosis are common. The patient may wake up after a single dose of naloxone, but the level of consciousness may deteriorate as the naloxone wears off in 30 to 90 minutes while the effects of methadone persist.

Gastrointestinal System

Delayed gastric emptying and paralytic ileus is possible.

Diagnosis of Methadone Overdose

Presumptive

A strong index of suspicion is necessary. If available, histories from the patient and from reliable third parties are invaluable. Empty bottles, if any, found with the patient may provide a clue as to the dose of medication taken and whether or not it was prescribed to the patient.

A response to naloxone indicates the presence of an opioid overdose. In a methadone overdose, a cumulative dose of up to 10 mg to 20 mg of naloxone may be required to reverse the coma or respiratory depression.

Confirmatory

Urine Toxicology:

Treatment must not be delayed while awaiting laboratory results, which could take four to 24 hours to be reported. Standard emergency toxicology immunoassay test kits do not detect methadone. The screen may be reported as "opiate negative" because methadone does not cross-react with the test antibody due to its unique chemical structure. If methadone overdose is suspected, methadone screening must be specifically requested.

Plasma Levels

Plasma levels are not useful for diagnosis or in guiding therapy due to the wide inter-individual variation in tolerance to methadone. Blood concentrations associated with fatalities attributed to methadone overlap with those found in methadone-maintained subjects (Merrill et al., 1996). Therapeutic levels associated with stability are 0.49 µMOL/L or more for trough levels. Methadone levels above 1.29 µMOL/L are desirable because they block the effects of heroin (Loimer & Schmid, 1992). A patient on a methadone treatment program was prescribed a daily dose of 195 mg per day with a peak level of 2.52 µMOL/L and trough of 0.92 µMOL/L with a half-life of only 17 hours (B. Kapur, personal communication, 1998). This patient, like many others, showed no evidence of intoxication but in fact complained of opioid withdrawal symptoms 15 hours later. Also, if the ratio of serum methadone metabolite to parent compound is less than one, it indicates intolerance to methadone. The converse is true in methadone-tolerant patients (Garriott et al., 1973). It should be noted that post-mortem levels vary depending upon the site of collection (Levine et al., 1995) and can vary five-fold. Also, the liver can release methadone into the blood stream both before and after death (Kreek et al., 1978), thereby elevating blood levels (Benbow et al., 1996). The table below (adapted from Drummer et al., 1992) summarizes serum levels associated with methadone fatalities to show the wide range of fatal levels.

Serum Levels Associated with Methadone Fatalities

RANGE (µMOL/L)	MEAN (µMOL/L)	Reference
0.19–1.6	0.84 (n=18)	Segal & Catherman (1974)
0.6–9.7	4.2 (n=10)	Robinson & Williams (1971)
1.3–5.8	3.2 (n=10)	Manning et al. (1976)
1.2–3.2	1.9 (n=4)	Norheim (1973)
0.87–8.1	2.1 (n=10)	Drummer et al. (1992)
0.64–6.1	1.8	Clark et al. (1995)
2.6	N/a (n=1)	Hendra et al. (1996)

Treatment of Methadone Overdose

All patients with a methadone overdose with respiratory depression should be admitted to hospital. If there is need for naloxone infusion, admission to the ICU is necessary (Finfer, 1996). In the first 24 hours, patients should also be monitored for the development of NCPE or ARDS. Patients may have to be held against their will, especially if they require naloxone infusion.

Airway and Ventilation

It is important to establish a patent airway and adequate ventilation. Oxygen by bag valve mask should be administered. Intubation is necessary if:

- respirations are inadequate
- persistent desaturation despite supplemental oxygen is present
- hypercapnea develops
- patient fails to respond to naloxone in two minutes.

Position the patient in the left lateral decubitus before giving naloxone because of withdrawal-induced emesis that might result.

Specific Antidote: Naloxone

Naloxone is a pure opioid antagonist that reverses the respiratory depressant effects of opioid agonists by competitively binding at μ receptors site. The onset of action is within one to two minutes after intravenous administration and within two to five minutes if given by intramuscular or subcutaneous routes. The peak effect is between five and 15 minutes. The half-life is about 30 to 100 minutes (Fishman et al., 1973). However, the duration of action may only be up to 60 minutes. Naloxone also reverses euphoria, analgesia, sedation, GI stasis and urinary retention caused by opioids. Naloxone can precipitate severe withdrawal in opioid-dependent patients, including in those on methadone maintenance.

Bolus Dose(s):

In Comatose Patients with Respiratory Depression

Infants and children less than five years or less than 20 kg:

The recommended initial dose is 0.01 mg/kg, followed by 0.1mg/kg if no response is elicited within two minutes (Moore et al., 1980).

Adults and children older than five years or more than 20 kg:

The initial dose should be 2.0 mg intravenously. If no response is achieved, a further 2 to 4 mg of naloxone should be repeated every two to three minutes (Abbott Laboratories Ltd. 1996) until a total dose of 10 to 20 mg has been given. If no response is elicited, consider other causes of coma.

If vascular access is not possible, intralingual (Maio et al., 1987) endotracheal (Greenberg, 1984), intramuscular, subcutaneous (Wanger et al., 1998) or intranasal (Loimer et al., 1994) routes can be used. However, absorption from intramuscular or subcutaneous sites may be erratic.

In Comatose Patients without Respiratory Depression

The initial dose should be lower — 0.1 to 0.8 mg intravenously to diagnose opioid overdose. Thereafter the dose can be increased as above if no response is elicited. Care should be taken not to induce severe acute withdrawal in opioid-dependent patients.

Naloxone Infusion

Due to the long half-life and terminal elimination phase of methadone, repeated boluses of naloxone are required. However, this can cause the methadone-maintained patient to swing repeatedly between cycles of intoxication and withdrawal. The aim of treatment is to reverse the respiratory depressant effect without causing opioid withdrawal while the methadone is eliminated from the body. An infusion of naloxone allows for close titration of dose, thereby providing smooth control of symptoms (Goldfrank et al., 1996; Waldron et al., 1973).

Infusion Dose

Following an adequate bolus to reverse opioid overdose, infusion of two-thirds of the bolus dose per hour should keep the patient alert. In addition, one-half of the bolus dose should be administered (as a bolus) 15 to 20 minutes after the start of the infusion to prevent a drop in naloxone levels (Goldfrank et al., 1996).

Concentration and Rate of Infusion

Naloxone is compatible with sodium chloride 0.45 per cent and 0.9 per cent, or dextrose 5 per cent (D5W) solutions for intravenous infusion. Naloxone is not to be mixed with other drugs. A common formulation is 4 mg (i.e., contents of a 10 mL multi-dose vial of 0.4 mg/mL) in 250mL D5W to minimize fluid overload. The rate of infusion is usually 25 to 50 mL/hr = 0.4–0.8mg/hr. Unused solution must be discarded after 24 hours.

Monitoring

The patient's level of consciousness, respiratory rate and depth should be monitored during the infusion and for several hours thereafter. One author suggested a 72-hour admission with pulse oximetry monitoring for 24 hours after the infusion is discontinued (Hendra et al., 1996). However, pulse oximetry is only useful in detecting hypoventilation if the patient is not receiving supplemental oxygen, and it may provide a false sense of security (Hutton & Clutton-Brock, 1993) while using valuable resources (Nichol et al., 1996).

Titration

Respiratory or CNS depression should prompt an increase in the rate of naloxone infusion.

If the patient develops withdrawal, the infusion can be held until symptoms abate. If the infusion needs to be restarted owing to reappearance of toxicity, a lower rate of infusion should be used. Plasma naloxone or methadone levels are not useful in guiding treatment and should not be ordered.

Duration of Infusion

The exact duration of infusion needs to be titrated to the response of the patient. One author recommends stopping after 12 to 24 hours, with the patient monitored closely for several hours thereafter. Any deterioration in the level of consciousness, respiratory rate and depth necessitates resumption of the naloxone infusion with an initial bolus as required (Nichol et al., 1996). In one fatality, the patient died 44 hours after overdose and approximately three hours after the naloxone infusion was stopped (Hendra et al., 1996). In a 13-year-old female, a dose of 0.65 mg/kg was used over 65.5 hours of continuous infusion with full recovery (Romac, 1986). Naloxone has been given to infants for as long as five days without ill effect, resulting in complete recovery (Tenenbein, 1984)). The end point of the infusion should be adequate spontaneous respiration, an alert and awake patient, dilated pupils and adequate oxygenation.

Monitoring Post-infusion

Little data exist on the duration of monitoring in the ICU after naloxone is discontinued. The patient should be monitored for an additional eight to 12 hours for recurrence of toxicity (C. Rodriguez, personal communication, 1998). On the general medical floor, the patient should be observed for evidence of re-narcotization for at least another 12 hours. If the patient is alert, breathing normally and ambulating without supplemental oxygen, it is unlikely that significant hypercapnia is present.

Toxicity of Naloxone

Toxin-induced CNS depression and even coma are usually well tolerated if treated early. According to Hoffman and Goldfrank, artificially induced arousal does not necessarily improve prognosis (Hoffman & Goldfrank, 1995). In the same review, they cite case reports of pulmonary edema, hypertension, seizures, arrhythmias and cardiac arrest following naloxone administration. Also there is some risk to the patient and clinician through the precipitation of violence by inducing opioid withdrawal.

In a prospective study, 1.3 per cent (95 per cent confidence interval, 0.4 per cent–3 per cent) of the 453 intoxicated patients presenting to the ER had the following adverse effects within 10 minutes after naloxone administration (one asystole, three generalized convulsions, one pulmonary edema and one violent behaviour). No further complications were observed after 10 minutes (Osterwalder, 1996). However, Hoffman and Goldfrank (1995) also cite several other studies that report on the safety of naloxone. Therefore, it must be concluded that naloxone is relatively safe.

Gastrointestinal Decontamination

Ipecac should be avoided due to the risk of aspiration pneumonia. Gastric lavage may be of benefit since methadone delays gastric emptying and some of the ingested drug may be aspirated. However, it is important to protect the airway before this is attempted. Activated charcoal should also be given. Methadone is fully absorbed in two to four hours. Therefore, gastrointestinal decontamination should not be attempted beyond four hours post ingestion.

Special Considerations

- Often the patient may have consumed other drugs — notably alcohol, cocaine and sedative hypnotics. Withdrawal states from alcohol and opiates, and intoxicated states due to stimulants (cocaine and amphetamines), are hyperadrenergic states. Caution should be exercised in using naloxone in these mixed overdose states due to the risk of arrythmias, especially if there is underlying heart disease. In such situations, it might be appropriate to intubate and mechanically assist ventilation while awaiting natural elimination of the drug (Hoffman and Goldfrank, 1995).
- Restraints might be needed to prevent violent behaviour and should be considered before reversing opioid overdose.
- If the patient wants to leave before being completely reversed, it may be necessary to certify the patient.
- Nalmaphene, a long-acting opioid antagonist, shows some promise in the reversal of toxicity from long-acting opioids in non-tolerant individuals (Wang et al., 1998). However, further research is necessary before it can be used widely in emergency situations. It is not currently available in Canada.

Instructions on Discharge

- The patient and caregivers should be warned about the risk of recurrence of

overdose even without additional drug use. The patient should return to hospital if feeling excessively drowsy or if the family has any difficulty waking the patient. The patient should abstain from alcohol and other drugs if possible. He or she might be especially sensitive to opioids and might experience another overdose if using the usual amount of drug.

- The patient should be referred to an appropriate treatment program if an underlying addiction exists.
- If the patient is in a methadone maintenance treatment program, the prescribing physician should be informed about the overdose.

Conclusion

Methadone availability is increasing and physicians must be able to diagnose and effectively manage methadone overdose. Methadone intoxication is characterized by prolonged CNS and respiratory depression. It usually requires naloxone infusion and admission to the ICU until spontaneous respiration is adequate and the patient is alert. Extra precautions must be taken in poly-drug overdose and in opioid-dependent patients to prevent toxicity from naloxone. Monitoring for recurrence of overdose is necessary, and naloxone infusion may have to be restarted. Appropriate interventions should be instituted to prevent overdose in the future. The prevention and reduction of methadone-related deaths from overdose will greatly enhance the net effectiveness of methadone maintenance for the treatment of opioid dependence.

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Carmina Vieria-Conti
Complaints Officer
Patient Relations Programs
Ontario College of Pharmacists

ENDING THE PHARMACIST/PATIENT RELATIONSHIP*

How can I end a pharmacist/patient relationship with one of my patients without being accused of "abandonment?"

You may, at some point in your career, be faced with the difficult decision of having to terminate your professional relationship with one of your patients. While pharmacists are empowered with the ability to exercise their professional judgment and can choose to terminate a pharmacist/patient relationship, members need to consider paragraph six of the Professional Misconduct Regulation made under the *Pharmacy Act*. It defines one ground of professional misconduct as: "Discontinuing professional services that are needed, without reasonable cause, unless, i) the patient requests the discontinuation, ii) alternative services are arranged, or iii) the patient is given a reasonable opportunity to arrange alternative services."

As you have accepted responsibility for providing pharmaceutical care to the patient, your relationship with the patient should not end without good reason, proper notice and an opportunity to obtain another pharmacist's (pharmacy's) services. While the reasons for ending a professional relationship vary, the following general suggestions may be helpful to pharmacists when their judgment tells them that it will be in the patient's best interest to terminate the pharmacist/patient relationship.

1. **Communicate your decision to the patient verbally.** This should be done in a private manner. Some pharmacies have patient counselling booths/areas. If this is not available in your current employment situation, take the patient aside from other

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patients and employees to discuss your decision and reasons. Be as compassionate, supportive and clear as possible. Advise the patient that this decision will be communicated to his or her physician if any future verbal prescriptions are called in. This will show that you are committed to your decision and it will also afford the patient an opportunity to advise his/her doctor personally. In some cases, the patient may become upset and may argue with you. Be prepared and refrain from entertaining any argument by reciprocating — chances are, the argument will be short lived if you avoid engaging in a debate.

2. Give the patient a reasonable amount of time to find a new pharmacy. There is no set amount of time you should give, as this will vary depending upon the availability of services in your area. Offer the patient some suggestions as to other pharmacies in the area and assure the patient that you will transfer his or her prescription records to their new pharmacy of choice. Tell the patient that you will make the transition as easy as possible for him or her. If no outstanding prescriptions remain on file at your pharmacy, provide the patient with a patient profile report/medication history for his or her information.

3. Documentation. Put your decision in writing and give the letter to your patient at the time of your discussion. Make a note on the patient profile, and retain a copy of the letter to the patient. Remember, if it isn't documented, it didn't happen. A sample letter you may consider using when terminating a pharmacist/patient relationship is included with this article. Please note that the letter should be signed by either the designated manager of the pharmacy or the owner of the pharmacy.

4. Advise Your Staff. Let each member of your dispensary and front shop staff know that you have made this decision. If the patient returns to the pharmacy and seeks to obtain pharmaceutical care services, speak to the patient privately and, if necessary, again go over the reasons for terminating the relationship. Remember, be compassionate and avoid any arguments. Offer to make another copy of the letter for the patient.

In summary, a pharmacist may discontinue the professional services to a patient as long as:

- alternative services are arranged for the patient, or
- the patient is given a reasonable opportunity to arrange alternative services, or
- the patient requests the discontinuation.

We hope these suggestions will assist pharmacists faced with this difficult decision.

SAMPLE LETTER FOR TERMINATING A PHARMACIST/ PATIENT RELATIONSHIP

Dear (patient name),

As we discussed, I do not believe that it is in your best interest for (name of pharmacy) to continue as your pharmaceutical care provider. I regret to inform you that the pharmacists at (name of pharmacy and address) will no longer be in a position to provide you with professional services, after (date you have chosen as the last day of care).

Please obtain the services of another pharmacy, satisfactory to you, at your earliest convenience. Please also advise your physician that prescriptions, written or verbal, will no longer be filled for you at our pharmacy after (date of last day of care). We feel that this information should be communicated to your physician's office by you directly.

Once you have chosen a new pharmacy, please have them contact us at (your pharmacy's phone number). We will be happy to transfer all of your prescription records to your new pharmacy. I have enclosed a copy of your patient profile that documents your medication history for (length of time patient profile covers).

Sincerely,

_____

Designated Manager
or Owner of Pharmacy

Anne Kalvik, BSc Phm
Eva Janecek, BSc Phm
and Pearl Isaac, BSc Phm

USE OF METHADONE FOR THE TREATMENT OF CHRONIC PAIN

Summary

Methadone should not be used in the routine management of acute pain. "*Methadone is generally recommended as a second-line opioid only which should be prescribed exclusively under the supervision of experts in pain management and palliative care*" (Librach, 1997).

Methadone is a potent opioid analgesic with primarily μ opioid activity. It has no active metabolites (Bruera & Fainsinger, 1997; Ripamonti et al., 1997) of clinical significance. It is well absorbed when given orally (Reisine & Pasternak, 1996).

As an analgesic, methadone can be difficult to titrate since there are great individual variations in response to dose (both initial and final) and dosage frequency.

One of the benefits of methadone is its long duration of action after oral administration. The average plasma half-life is 15 to 40 hours (Reisine & Pasternak, 1996). However, some opioids such as morphine and oxycodone are now available in controlled-release formulations that offer long action without the risk of delayed accumulation that may occur with the use of methadone; preparations such as these may be preferable.

For the treatment of *Opioid Dependence*, methadone typically has a duration of action of at least 24 hours and can in most cases be given once daily. However, for the treatment of pain, the duration of action is usually shorter. Although some individuals can be managed on once-daily dosing, methadone is more frequently given every eight or 12 hours for pain.

Resulting accumulation due to methadone's long half-life can expose patients to unexpected severe toxicity (Librach, 1997), for example, CNS and respiratory depression, especially in the elderly or debilitated patient (Abramowicz, 1998).

The relative potency of methadone may also increase in relation to the duration of previous opioid treatment (Bruera & Fainsinger, 1997). There is great individual variation in dose (Gardner-Nix, 1996) and, at times, a general underestimation of methadone potency (Lawlor et al., 1998). Safe use of methadone for pain requires extremely careful and individualized patient monitoring.

It is recommended that clinicians who have little experience with the use of methadone be cautious when considering prescribing it for pain. Appropriate medical references should be reviewed and experienced colleagues consulted when a patient is prescribed methadone for the first time (National Cancer Institute, 1999.)

If appropriate, concomitant use of non-opioid therapies (both pharmacologic and non-pharmacologic) should be considered.

Much of the published literature describes the use of methadone in cancer pain rather than in chronic non-malignant pain (Lawlor et al., 1998; Ripamonti et al., 1998).

Methadone used for appropriately selected patients and prescribed by an experienced clinician can offer effective analgesia with a long duration of action at low cost (Garnder-Nix, 1996; O'Rourke et al., 1996).

Prescribing Issues

On the occasion when methadone is prescribed, it is used as an alternative to morphine in the treatment of severe chronic pain (McEvoy, 1999; Parfitt, 1999). It may offer improvement in pain relief for those who are opioid-resistant (Gardner-Nix, 1996), tolerant to morphine (Abramowicz, 1998; Morley et al., 1993) or experiencing CNS toxicity from active metabolites of other opioid analgesics (Ripamonti et al., 1997). It may be useful for those individuals who experience excitation or exacerbation of pain with morphine (Parfitt, 1999; Morley et al., 1993). Some clinicians feel that the use of methadone for pain should be limited to the rare patient who is truly allergic to morphine and that methadone may have a role to play in "opioid rotation," since there may be less chance of tachyphylaxis occurring (Gardner-Nix, 1996; Librach, 1997).

Methadone has been given orally, rectally or by subcutaneous (s.c.) injection. Although there is disagreement on this issue, if repeated injections are required the intramuscular (i.m.) route may be preferred to s.c. (Parfitt, 1999), because local

toxicity (tissue irritation) has been reported with s.c. methadone (Bruera et al., 1991). Relative intramuscular to oral ratio is about 1:2 (Cherny, 1996). Oral efficacy of methadone may be particularly useful for those who cannot be maintained on long-term injectable opioids due to tissue necrosis (Gardner-Nix, 1996). For patients unable to take methadone orally, extemporaneously prepared methadone rectal formulations may be considered (Ripamonti et al., 1997). Methadone has been administered through a colostomy in those with rectal resections (Fainsinger, 1999). It has also been given intravenously (National Cancer Institute, 1999).

Opioid equivalency tables should be used *with caution* to calculate methadone dose. Although these tables are based on analgesic efficacy, they often reflect single-dose situations and may not apply to long-term treatment. Also, they are unreliable because of methadone's high individual variations in bioavailability, cross-tolerance and half-life. The relative potency of methadone to morphine may be five to 10 times greater than the values published in many tables (Bruera & Fainsinger, 1997), especially in patients who are receiving prolonged therapy with other opioids. Some clinicians suggest that for effective analgesia in opioid-naive patients or in use of methadone as the initial opioid, relatively higher doses of methadone may be required (but still at lower doses than suggested by many equianalgesic tables) (Ripamonti et al., 1998). In single-dose studies, methadone may be slightly more potent than morphine, but in repeated dose situations, it can be many times more potent (Cherny, 1996). Some switch-overs to methadone in which standard equivalency tables were used as a reference have resulted in respiratory depression and non-cardiogenic pulmonary edema (Hunt & Bruera, 1995). Some clinicians recommend that patients who are switched to methadone should be given 1/10 of the equivalent morphine dose (Bruera & Fainsinger, 1997). It has been recommended that doses be gradually increased over four to six days while the dose of the other opioid is being decreased (Fainsinger et al., 1993), with frequent assessment of sedation and analgesia. *Frequent monitoring is necessary to prevent serious side-effects.*

Starting doses of methadone should be low in order to facilitate identification of toxic effects, particularly sedation. Methadone dose and/or dosage frequency may need to be decreased as the final effective analgesic dose is approached (Levy, 1997; Gardner-Nix, 1996; Levy, 1996). Giving methadone "when needed" at the beginning of treatment may help to minimize dose accumulations and overshoot seen with fixed dosing intervals (Cherny, 1996). Initial analgesic doses of methadone may start from 2.5 to 10 mg given at intervals of three to 12 hours, depending on the pain and adjusted according to response. Others suggest starting doses of 10 to 20 mg (Abramowicz, 1998). Many clinicians feel strongly that initial

daily doses should not exceed 30 mg/day due to the risk of cumulative toxicity. Much higher final doses have been used in clinical practice after careful titration (Gardner-Nix, 1996).

The analgesic effect of methadone begins about 10 to 20 minutes after parenteral injection and about 30 to 60 minutes after oral administration. Duration of analgesia after single doses is four (Parfitt, 1999) to eight hours, but it may be considerably longer following repeated dosing (USP DI, 1998; Parfitt, 1999). Unfortunately this may increase unpredictably with repeated dosing (Librach, 1997) and may be the cause of difficulty in titrating the drug in some individuals. Some clinicians feel that methadone should never initially be given more frequently than every eight hours when patients are being switched from other high-dose opioid therapy (Fainsinger et al., 1993). The duration of action of analgesia is in marked contrast to the duration of action in preventing opioid withdrawal symptoms which, at steady state, is approximately 24 hours. Opinions vary regarding suitable dosage intervals for analgesia. The duration of action may decrease as tolerance develops during chronic therapy (USP DI, 1998). Once optimal analgesic dose has been established, methadone is most commonly given every eight or 12 hours (Parfitt, 1999; Fainsinger, 1999). However, some patients can be managed with once-daily dosing (Fainsinger, 1999).

Some clinicians prefer to treat break-through analgesia with shorter-acting analgesics, such as morphine or hydromorphone, due to the concern that methadone's long half-life makes it less safe for this purpose (Gardner-Nix, 1996). However, other physicians with extensive experience with methadone have used it successfully in these circumstances as well (Fainsinger, 1999).

For patients with both pain and chemical dependence, it is important to identify the predominant problem and treat it first. If the addiction problem is not under control, pain will typically not respond even to aggressive opioid treatment. It is also useful to keep in mind that factors such as anxiety and stress may adversely affect pain control. Treatment other than an increase in methadone dose should be explored in such cases.

The illicit use, or diversion, of methadone exists as a possibility even in patients on methadone for chronic pain conditions. These patients typically take home a large supply of methadone to last from one to four weeks.

A number of drug interactions have been described with methadone (See Chapter 11). Any medication with opioid antagonist activity (e.g., nalbuphine,

pentazocine, butorphanol) is contraindicated, since it may precipitate withdrawal in a patient receiving methadone on a regular basis.

In the future, N-methyl-D-aspartate (NMDA) receptor antagonists (dextromethorphan, ketamine and others) may have a role to play in the treatment of pain. They may act to potentiate opioid effects and reduce the development of tolerance. To date, such effects have been demonstrated with morphine (Weisenfeld-Hallin, 1998). It is possible that research may provide evidence that this is true of methadone as well.

Authorization

Physicians wanting to prescribe methadone for pain need to obtain authorization. Physicians must apply directly to the Office of Controlled Substances (OCS) for authorization to prescribe for pain.

Pharmacists can check whether a physician is authorized to prescribe methadone for pain either by asking the physician or by contacting OCS (613-946-5139).

Dispensing of Methadone for Pain

As for all other medications, pharmacists need to be familiar with the medication and its safe use.

Whenever possible, it is preferred that if methadone is being prepared in an oral liquid dosage form, it be dispensed diluted with orange drink (see Chapter 5) or another suitable vehicle, such as simple flavoured syrups (Parfitt, 1999).

Avoid dispensing methadone-in-water solutions directly to patients.

It is important to maximize safety by taking precautions both to minimize errors in measuring doses and to limit the possibility of intravenous injection.

USP DI recommends that in the treatment of chronic pain, each methadone dose should be diluted to at least 30 mL.

Since methadone is a very potent opioid, there may be very serious consequences due to errors in measurement, especially if very concentrated preparations are prescribed or dispensed. When dispensed in a multidose bottle, methadone should be dispensed in concentrations that are practical with respect to individual doses and total doses

prescribed. At the same time, the concentrations should ensure patient safety and minimize the possibility of inadvertent overdose or underdose due to errors in measuring. The pharmacist and the physician can determine what is the safest and most practical concentration.

Oral syringes or special calibrated droppers have been used to accurately measure doses at home.

Some chronic pain patients find the bitter taste of methadone particularly problematic. Applesauce or a candy taken after the dose may help to alleviate this (Gardner-Nix, 1996). Alternatively, methadone has been extemporaneously compounded into oral capsules or rectal suppositories, but only for the treatment of pain (not for opioid dependence).

Childproof closures (safety caps) should be used.
Recommended auxiliary labelling:

- Include usual cautionary statements regarding risk of death to children and non-tolerant adults.
- "May cause drowsiness."
- "Avoid alcoholic beverages."

Patient dialogue should emphasize safe and secure storage of methadone. Patients should be advised to contact their physician (or pharmacist) if excess sedation is experienced or observed by the family. (For a discussion of adverse effects, see Chapter 10.)

As with all other opioids and psychoactive medications, patients should be assessed for excessive sedation or cognitive impairment, early refills, unauthorized or uncontrolled escalation of doses, acquisition of medications from more than one physician, etc.

Concerns should be communicated to the patient and physician(s).

Whenever possible, it is preferred that one physician be responsible for prescribing all opioid and psychoactive medication and that one pharmacy be responsible for dispensing them.

The physician and pharmacist should communicate regularly to discuss the above and any other relevant issues.

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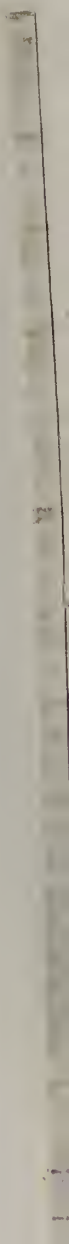

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